**SECTION 2.7**
**CLINICAL SUMMARY**

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**SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY**

# EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (FTC/RPV/TAF FDC)

Gilead Sciences

18 June 2015

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| ACTH | adrenocorticotropic hormone |
| ADME | absorption, distribution, metabolism, and excretion |
| ADR | adverse drug reaction |
| AE | adverse event |
| aGFR | actual glomerular filtration rate |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ATR | efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®) |
| ATV | atazanavir |
| AZT | zidovudine |
| BE | bioequivalence |
| BMD | bone mineral density |
| BMI | body mass index |
| CCDS | company core data sheet |
| CD4 | cluster determinant 4 |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| CKD | chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate |
| $CL_{cr}$ | creatinine clearance |
| COBI, C | cobicistat (Tybost®) |
| CSR | clinical study report |
| C-telopeptide, CTx | type I collagen C-telopeptide |
| CV | coefficient of variation |
| CYP | cytochrome P450 enzyme |
| D/C/F/TAF | darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated) |
| d4T | stavudine |
| DAIDS | Division of AIDS |
| DDI | drug-drug interaction |
| DEXA, DXA | Dual Energy X-ray Absorptiometry |
| DRV, D | darunavir |
| DSPH | Drug Safety and Public Health |

| | |
|---|---|
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated) |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EFV | efavirenz |
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| $eGFR_{CKD\text{-}EPI,\ cysC}$ | estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation |
| $eGFR_{CKD\text{-}EPI,creatinine}$ | estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation |
| $eGFR_{creat}$ | estimated glomerular filtration rate for creatinine as calculated by MDRD formula |
| $eGFR_{cyst}$ | estimated glomerular filtration rate for cystatin C as calculated by the Hoek formula |
| EU | European Union |
| EVG, E | elvitegravir (Vitekta®) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDC | fixed dose combination |
| FEPO4 | fractional excretion of phosphate |
| FEUA | fractional excretion of uric acid |
| FTC, F | emtricitabine (Emtriva®) |
| FTC/RPV/TDF | emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera® and Eviplera® when coformulated) |
| GFR | glomerular filtration rate |
| GGT | gamma-glutamyl transferase |
| Gilead | Gilead Sciences |
| GLSM | geometric least-squares mean |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| HLGT | high-level group term |
| HLT | high-level term |
| HR | heart rate |
| INSTI | integrase strand-transfer inhibitor |
| ISS | Integrated Summary of Safety |
| ITT | intent-to-treat |
| LDL | low-density lipoprotein |
| LDV/SOF | ledipasvir/ sofosbuvir (coformulated; Harvoni®) |
| LLT | lower-level term |

| | |
|---|---|
| LOCF | last observation carried forward |
| LPV | lopinavir |
| LSM | least-squares mean |
| M = E | missing = excluded |
| M = F | missing = failure |
| MDRD | Modification of Diet in Renal Disease |
| MDZ | midazolam |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N(t)RTI | nucleoside (tide) reverse transcriptase inhibitor |
| NCEP | National Cholesterol Education Program |
| NIAID | National Institute of Allergy and Infectious Disease |
| OATP | organic anion transporting polypeptide |
| OH | hydroxyl |
| P1NP | procollagen type 1 N-terminal propeptide |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PD | pharmacodynamic(s) |
| P-gp | P-glycoprotein |
| PI | protease inhibitor |
| PK | pharmacokinetic(s) |
| PRT | proximal renal tubulopathy |
| PSUR | Periodic Safety Update Report |
| PT | preferred term |
| PTH | parathyroid hormone |
| Q1, Q3 | first quartile, third quartile |
| QT | electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected for heart rate using Bazett's formula |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RAM | resistance-associated mutation |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |
| RPV | rilpivirine; TMC278 (Edurant®) |
| RTV | ritonavir |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBR | stay on baseline regimen |
| SD | standard deviation |
| SE | standard error |
| SOC | system organ class |

| | |
|---|---|
| ST segment | period when the ventricles are depolarized |
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| STR | single-tablet regimen |
| TAF | tenofovir alafenamide |
| TBLH | total body less head |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TFV | tenofovir |
| TFV-DP | tenofovir diphosphate |
| TMC | Tibotec Medicinal Compound |
| TmP/GFR | renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate |
| tQT | thorough QT |
| TVD | emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®) |
| UACR | urine albumin to creatinine ratio |
| UPCR | urine protein to creatinine ratio |
| US, USA | United States |
| vs | versus |

## PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| AUC | area under the plasma/serum concentration versus time curve |
| AUC24h | area under the plasma concentration-time curve from time of intake up to 24 hours after dosing |
| $AUC_{last}$ | area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration |
| $AUC_{inf}$ | area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$ |
| $AUC_{tau}$ | area under the plasma/serum concentration versus time curve over the dosing interval |
| $CL_{iohexol}$ | iohexol clearance |
| $C_{max}$ | maximum observed plasma/serum concentration of drug |
| $C_{tau}$ | observed drug concentration at the end of the dosing interval |
| $C_{trough}$ | plasma concentration at the end of the dosing interval |
| $IC_{xx}$ | concentration that results in xx% inhibition |
| $t_{1/2}$ | estimate of the terminal elimination half-life of the drug in serum/plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant ($\lambda_z$) |
| $T_{max}$ | time (observed time point) of $C_{max}$ |

## INTRODUCTION

Human immunodeficiency virus, type 1 (HIV-1) infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide {27071}. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral (ARV) therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression.

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS-associated comorbidities. Clinical attention has become more focused on optimizing tolerability, long-term safety, and adherence {29705}. There remains a significant medical need for safe and effective new therapies that take into consideration the aging patient population, non-HIV-related comorbidities, virologic resistance, and regimen simplification.

For ART-naive, HIV-infected patients, initial therapy generally consists of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) in combination with a third active ARV from one of 3 drug classes: an integrase strand-transfer inhibitor (INSTI); a nonnucleoside reverse transcriptase inhibitor (NNRTI); or a protease inhibitor (PI) with a pharmacokinetic enhancer. Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {32519}, {27621}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an approved oral prodrug of TFV. The combination of emtricitabine (FTC; F) and TDF forms a N(t)RTI backbone in several once-daily fixed dose combinations (FDCs): Truvada® (FTC/TDF), Complera® or Eviplera® (FTC/rilpivirine[RPV]/TDF), Atripla® (efavirenz/FTC/TDF), and Stribild® (elvitegravir [EVG; E]/cobicistat [COBI; C]/FTC/TDF). While these TDF-containing products are used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk of TDF therapy, which also is associated with reductions in bone mineral density that are larger than those observed with other NRTIs used in ARV regimens {26885}.

Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF. It provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate, and > 90% lower circulating levels of TFV relative to TDF. TAF has demonstrated an improved bone and renal safety profile compared with TDF in clinical studies, which is attributed to lower plasma TFV exposures compared to the approved dose of TDF.

Rilpivirine (referred to interchangeably as RPV, TMC278, or R278474), a diarylpyrimidine derivative, is a potent NNRTI with in vitro activity against wild type HIV-1 and NNRTI-resistant mutants. RPV is available as a single agent (Edurant®) and as the FDC Complera/Eviplera (FTC/RPV/TDF; 200/25/300 mg). Rilpivirine, in combination with other ARVs, provides a safe and effective alternative ART option with an improved tolerability profile over other NNRTIs.

Gilead has coformulated TAF with FTC and RPV into an FDC tablet, FTC/RPV/TAF (200/25/25 mg) for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older without any known mutations associated with resistance to the individual

components of FTC/RPV/TAF. This marketing application for FTC/RPV/TAF is based on a pivotal bioequivalence study (GS-US-366-1159) that demonstrated the following:

- Bioequivalence of TAF and FTC exposures between the FTC/RPV/TAF FDC (200/25/25 mg) and Gilead's FDC tablet containing the HIV-1 INSTI EVG, the pharmacoenhancer COBI, FTC, and TAF (E/C/F/TAF 150/150/200/10 mg), thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the FTC/RPV/TAF FDC to those from E/C/F/TAF.

- Bioequivalence of RPV exposure between the FTC/RPV/TAF FDC tablet and the marketed product Edurant (RPV 25-mg tablet), thereby supporting extrapolation of the demonstrated safety and efficacy of RPV exposures in the FTC/RPV/TAF FDC to those from Edurant.

In accordance with the bioequivalence approach outlined above, the safety and efficacy of FTC/RPV/TAF in various patient populations is supported by the safety and efficacy of the individual components in those populations as follows:

- ART-naive adult subjects

  — Two pivotal Phase 3 studies conducted with E/C/F/TAF (Studies GS-US-292-0104 and GS-US-292-0111)

  — Two pivotal Phase 3 studies conducted with RPV in combination with an N(t)RTI backbone, which may have included FTC and TDF (Studies TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]). For this marketing application, the FTC/TDF subset is presented for these studies because it provides data for RPV and FTC administered with a TFV prodrug and, therefore, contains the most relevant data for the FTC/RPV/TAF combination.

- Virologically suppressed adult subjects

  — 1 Phase 3 E/C/F/TAF study (GS-US-292-0109)

  — Two Phase 2b or 3b FTC/RPV/TDF studies (GS-US-264-0111 and GS-US-264-0106)

- Adult subjects with mild to moderate renal impairment

  — 1 Phase 3 E/C/F/TAF study (GS-US-292-0112)

  — RPV is approved without dose adjustment for patients with mild to moderate renal impairment

- Adolescent subjects

  — One Phase 2/3 E/C/F/TAF study (GS-US-292-0106)

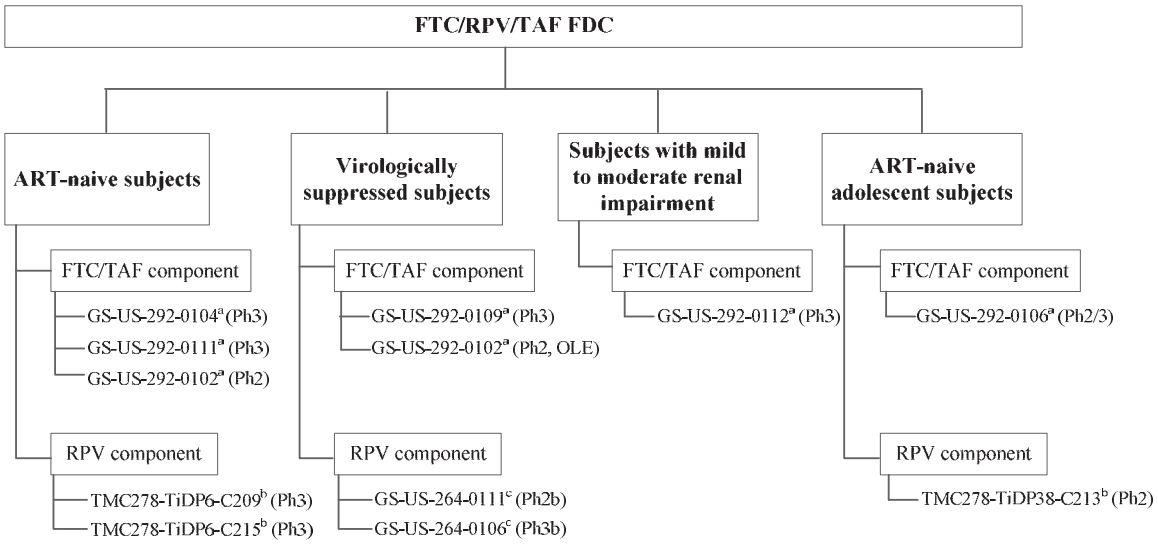
  — One 1 Phase 2 RPV study (TMC278 TiDP38-C213 [C213])

At the time of this submission, the studies conducted with E/C/F/TAF and the study of RPV in adolescent subjects (C213) are under review in multiple countries, including the US and EU, as parts of marketing applications. The studies conducted with RPV (with the exception of Study C213) or FTC/RPV/TDF have been previously reviewed by regulatory authorities in multiple countries, including the US and EU, leading to the current indications for these products.

The registration of FTC/RPV/TAF is also supported by a comprehensive package of clinical and nonclinical pharmacology data collected using the component agents (either alone or in combination) and by postmarketing data. Together, the data support the proposed prescribing information for the FTC/RPV/TAF FDC tablet.

This document is a summary of the primary safety data provided from multiple Phase 2 and 3 studies of E/C/F/TAF, RPV, or Complera/Eviplera in HIV-infected subjects (Figure 1). These data have previously been submitted and are summarized herein in the context of safety of the FTC/RPV/TAF FDC tablet. Supportive safety data are available from Phase 1 studies of FTC/RPV/TAF in healthy volunteers. Additional safety data (deaths, SAEs, and AEs leading to discontinuation) are provided from other Phase 1 studies of TAF.

**Figure 1. Primary Studies Supporting the Safety of FTC/RPV/TAF Across Patient Populations**




a E/C/F/TAF Study
b RPV Study
c Complera/Eviplera Study

## EXECUTIVE SUMMARY

### Exposure to Drug

No data are currently available from studies of FTC/RPV/TAF in HIV-1 infected patients. To date 197 healthy volunteers have received FTC/RPV/TAF in 3 Phase 1 studies.

Since exposures of the FTC and TAF components of the FTC/RPV/TAF FDC have been shown to be bioequivalent to E/C/F/TAF, the safety data for E/C/F/TAF can be extrapolated to the FTC/RPV/TAF FDC. Since exposure of the RPV component of the FTC/RPV/TAF FDC has been shown to be bioequivalent to Edurant, the efficacy data for RPV can be extrapolated to the FTC/RPV/TAF FDC. Therefore, evidence to support the clinical safety of FTC/RPV/TAF is provided by a comprehensive program of 6 clinical studies of E/C/F/TAF, 3 clinical studies of RPV, and 2 clinical studies of the RPV-containing regimen, Complera/Eviplera. The subset of patients receiving FTC/TDF (FTC in combination with a TFV prodrug) within the 2 RPV clinical studies in adults provides data for RPV and FTC administered with a TFV prodrug and, therefore, contains the most relevant data for the FTC/RPV/TAF combination.

Across the E/C/F/TAF Phase 2 and Phase 3 studies included in this submission, a total of 2394 subjects have received E/C/F/TAF with a median (first quartile [Q1], third quartile [Q3]) exposure of 48.1 weeks (42.3, 60.0).

In the RPV studies included in this submission, a total of 722 subjects received at least 1 dose of RPV (25 mg) including 686 subjects in the RPV Phase 3 studies and 36 subjects in the RPV Phase 2 study.

In the Complera/Eviplera studies included in this submission, a total of 518 subjects received at least 1 dose of Complera/Eviplera (200/25/300 mg), including 469 subjects in the Phase 3 study, and 49 subjects in the Phase 2b study. Cumulative patient exposure to Complera/Eviplera since first marketing approval in the US on 10 August 2011 to 28 February 2015 is estimated to be 206,654 patient years. The patient exposure is estimated from sales figures and will tend to overestimate exposure, due to accumulation of drug stocks at pharmacies/distributors.

In the other Phase 1 TAF studies included in this submission, a total of 371 subjects received at least 1 dose of TAF as a single agent or part of another FDC (F/TAF or E/C/F/TAF).

### Demographic and Other Characteristics of the Study Population

#### *E/C/F/TAF Studies*

Demographic and general baseline characteristics were generally similar between treatment groups within each E/C/F/TAF Phase 2 and 3 study. The median ages of adult subjects with normal renal function who were ART-naive or virologically suppressed were generally similar, ranging from 33 to 41 years. Subjects with mild to moderate renal impairment were older, with a median age of 58 years in Cohort 1 (ART-experienced subjects who switched to E/C/F/TAF; range: 24 to 82). Across studies, a total of 97 subjects were ≥ 65 years of age. The median age of adolescent subjects in Study GS-US-292-0106 was 15 years (range: 12 to 17).

Approximately 15% of subjects in the E/C/F/TAF pivotal ART-naive studies were women. With the exception of Study GS-US-292-0106, most subjects across studies were white or black. Subjects in Study GS-US-292-0106 were black (87.5%) or Asian (12.5%). The median body mass index (BMI) was generally similar across all studies (approximately 25 kg/$m^2$), except for adolescent subjects in Study GS-US-292-0106 (median [Q1, Q3] BMI 20.0 [18.1, 23.2] kg/$m^2$).

Baseline disease characteristics were generally similar between treatment groups within each E/C/F/TAF study. The median baseline estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) value was generally similar across ART-naive and virologically suppressed adult subjects, ranging from 105.7 to 117.0 mL/min. In subjects with mild to moderate renal impairment, the median (Q1, Q3) $eGFR_{CG}$ value was 55.6 (45.7, 62.4) mL/min among subjects who were virologically suppressed at baseline. In ART-naive adolescent subjects, the median (Q1, Q3) eGFR calculated using the modified Schwartz formula was 110.9 (95.8, 118.8) mL/min/1.73 $m^2$.

Across the Phase 3 E/C/F/TAF studies in adults with normal renal function, most subjects (>89%) had no graded proteinuria at baseline. In subjects with mild to moderate renal impairment, 9.5% of virologically suppressed subjects had Grade 2 proteinuria at baseline, and 23.1% of subjects had Grade 1 proteinuria at baseline. Among adolescent subjects, < 5% had proteinuria at baseline.

***RPV Studies***

Demographic characteristics for the FTC/TDF subset (ie, the subset of subjects receiving FTC/TDF in RPV Studies C209 and C215) were similar in the pooled RPV (RPV-containing regimen) and control (efavirenz [EFV]-containing regimen) group for all parameters and were similar to those for the overall pooled population (ie, all subjects [any regimen]). Of all the subjects enrolled and treated with RPV in the FTC/TDF subset, 78.5% were male and 62.3% were White. The median age was 36 years in both treatment groups. Demographic characteristics for the FTC/TDF subset were similar between the individual Phase 3 trials.

The majority of subjects in RPV Study C213 were black or African American (32/36 [88.9%] subjects) and 20/36 (55.6%) subjects were female. The median (range) age and weight at screening were 14.5 (12-17) years and 45.2 (33-93) kg, respectively. For the 20 female subjects, Tanner stage V was seen in 3 (15.0%) girls each for breasts and pubic hair. Fourteen (70.0%) of the 20 female subjects had had their first menses prior to baseline visit. For the 16 male subjects, Tanner stage V was seen in 2 (12.5%) boys each for pubic hair and genitalia.

***Complera/Eviplera Studies***

The majority of subjects in the safety analysis set for Study GS-US-264-0111 were male (91.8%), with an overall mean age of 38 years (range, 24 to 57 years); most were white (81.6%) or black (12.2%) and non-Hispanic/Latino (79.6%). The mean value for BMI at baseline was 26.9 kg/$m^2$. Mean creatinine clearance ($CL_{cr}$) by Cockcroft-Gault was 121.9 mL/min at baseline (range, 73.3 to 199.8 mL/min).

Demographic and baseline characteristics in Study GS-US-264-0106 were generally similar between the FTC/RPV/TDF and stay-on-baseline regimen (SBR) treatment groups. The majority of subjects were male (87.6%), with an overall mean age of 42 years (range, 19 to 73 years); most were white (76.7%) or black or African American (17.4%) and non-Hispanic/Latino (82.4%). The mean value (SD) for BMI at baseline was 25.9 (5.15) kg/m$^2$. Mean (SD) $CL_{cr}$ by Cockcroft-Gault was 109.2 (28.88) mL/min at baseline (range, 50.2 to 250.9 mL/min).

The majority of subjects were male (71.9%) and white (68.8%). At baseline, the median age was 32 years (range: 19 to 45 years), median (first quartile [Q1], third quartile [Q3]) BMI was 26.4 (23.8, 28.3) kg/m$^2$.

### *FTC/RPV/TAF Studies*

In Phase 1 Study GS-US-366-1159, the majority of subjects were male (71.9%) and white (68.8%). At baseline, the median age was 32 years (range: 19 to 45 years), median (first quartile [Q1], third quartile [Q3]) BMI was 26.4 (23.8, 28.3) kg/m$^2$. In Phase 1 Study GS-US-366-1651, the majority of subjects in the Safety Analysis Set were male (60.0%, 36 subjects). The median age was 36 years (range: 18−45). The majority of subjects were white (70.0%) and were Hispanic or Latino (78.3%). At baseline, the median (Q1, Q3) BMI was 26.0 (23.3, 27.3) kg/m$^2$. Within each cohort, there were no notable differences between the sequences groups in any demographic characteristic. Subgroup analysis showed a similar overall median BMI for males and females. In Phase 1 Study GS-US-366-1689, the mean age was 34 years with a range of 18 to 45 years. Overall, there were more males than females (30 males [71.4%] and 12 females [28.6%]). The majority of subjects were white (61.9%) and Hispanic or Latino (52.4%). The mean BMI at baseline was 27.3 kg/m$^2$ with a range of 22.8 to 29.9 kg/m$^2$.

## Adverse Events

### *E/C/F/TAF Studies*

The frequency and type of reported adverse events (AEs) were generally similar in ART-naive adults, virologically suppressed adults, adults with mild to moderate renal impairment, and ART-naive adolescents across all studies. The percentage of subjects reporting any AE was generally similar across studies, with somewhat lower percentages among virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109 and ART-naive adolescent subjects in E/C/F/TAF Study GS-US-292-0106. The overall incidence of AEs was similar between treatment groups within each randomized study.

Serious AEs (SAEs) were reported for a similar percentage of subjects in both treatment groups in the comparative E/C/F/TAF studies (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109) and were < 10% in the E/C/F/TAF group in each study. Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study.

***RPV Studies***

The occurrence rates of AEs, drug-related AEs, SAEs, deaths, Grade 3 to 4 AEs for the subjects in the FTC/TDF subset were similar to those in the overall population. Most AEs were Grade 1 or 2 in severity. Four of the 7 subjects who died during the trials received FTC/TDF; all 4 were in the control group. Similar to the overall population, the proportion of subjects experiencing AEs leading to permanent discontinuation was smaller in the RPV group (3.8%) than in the control group (8.6%) for the FTC/TDF subset. The AE profile in adolescent Study C213 was similar to that in adults.

***Complera/Eviplera Studies***

Analysis of data obtained from continued treatment with FTC/RPV/TDF in virologically suppressed, HIV-1 infected subjects for up to 48 weeks in Studies GS-US-264-0111 and GS-US-264-0106 did not reveal adverse reactions or changes in the tolerability profile (frequency, nature, or severity of AEs) inconsistent with the known safety profile of FTC/RPV/TDF.

***FTC/RPV/TAF Studies***

There were no Grade 3 or 4 AEs, deaths or SAEs reported in the Phase 1 studies with FTC/RPV/TAF. Only 1 subject permanently discontinued any study drug due to an AE related to ledipasvir/sofosbuvir (LDV/SOF) (nonserious, Grade 2 colitis) in Study GS-US-366-1689.

**Analysis of AEs by Organ System or Syndrome**

As TAF is associated with >90% lower systemic TFV exposure relative to that associated with TDF, less off-target TFV-associated toxicity was anticipated in subjects receiving E/C/F/TAF in the Phase 2 and Phase 3 randomized studies, including less impact on the nephrotoxicity and reduced BMD. Results from the Phase 2 Study GS-US-292-0102 (E/C/F/TAF) supported this, demonstrating that subjects receiving E/C/F/TAF relative to those receiving STB had less impact on BMD, bone turnover markers, serum creatinine, and tubular proteins (urine retinol binding protein [RBP] to creatinine ratio and beta-2-microglobulin to creatinine ratio). After the primary hypothesis of noninferior efficacy of E/C/F/TAF relative to STB was achieved in the E/C/F/TAF Phase 3 comparative studies, multiplicity adjustments were made for 4 safety endpoints with a fallback procedure in sequential order with prespecified 2-sided alpha levels: hip BMD, spine BMD, serum creatinine, and treatment-emergent proteinuria. Statistically significant differences favoring E/C/F/TAF over STB at Week 48 for all key secondary safety endpoints in ART-naive adults and virologically suppressed subjects were observed: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), change from baseline in treatment-emergent proteinuria (ART-naive subjects; $p = 0.022$), and change from baseline in EFV-related symptom assessment composite score (virologically suppressed subjects; $p < 0.001$).

Elevations in serum creatinine levels were observed in subjects receiving FTC/RPV/TDF in both Studies GS-US-264-0111 and GS-US-264-0106 (as described below). Similar increases in

creatinine were noted in the Phase 3 studies of RPV. The small mean increase in serum creatinine observed with FTC/RPV/TDF in the 2 studies is similar to that reported in the prescribing information for RPV-based regimens and is not considered to be clinically important {22839}.

***Bone Safety***

Bone safety was assessed in the E/C/F/TAF Phase 2 and Phase 3 studies and the Phase 3 RPV studies due to the accelerated bone loss seen in the HIV-infected population.

Fractures

Across all E/C/F/TAF studies, fractures were uncommon, balanced between treatment groups, the result of trauma, and considered by the investigator as unrelated to the study drugs; none resulted in permanent discontinuation of study drugs.

Bone Mineral Density

*E/C/F/TAF Studies*

Across all E/C/F/TAF studies in ART-naive subjects, subjects receiving E/C/F/TAF experienced significantly less BMD reduction than those receiving STB.

In the Phase 3 E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, statistical analysis using the fallback procedure confirmed significance using adjusted alphas. At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a clinically significant (> 3%) decrease from baseline in hip BMD (E/C/F/TAF 16.8%, STB 50.1%) and in spine BMD (E/C/F/TAF 26.5%, STB 45.8%).

Across E/C/F/TAF studies in virologically suppressed subjects, improvements in BMD were observed in subjects who switched from a TDF-based regimen. In subjects with renal impairment (Study GS-US-292-0112), hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF. In ART-naive adolescent subjects (Study GS-US-292-0106), mean changes from baseline of approximately 1.7% and 0.8% in spine and total body less head (TBLH) BMD, respectively, were observed at Week 24. Both spine and TBLH median (Q1, Q3) height-age adjusted BMD Z-scores were within the expected range for age.

*RPV Studies*

In RPV Studies C209 and C215, DXA substudies showed a small but statistically significant median decrease from baseline in BMD for both treatment groups (1.4% and 1.5% in the RPV group and 1.4% and 1.5% in the control group at Week 48 and Week 96, respectively). No statistically significant differences were observed between treatment groups.

### *Renal Safety*

Renal toxicity has been associated with TDF use, and COBI inhibits tubular secretion of creatinine, leading to an increase in serum creatinine and a decrease in eGFR without an effect on actual glomerular filtration rate (aGFR), therefore renal parameters were assessed in all Phase 2 and 3 studies with E/C/F/TAF and Complera/Eviplera.

Renal parameters were assessed in the Phase 2 and 3 studies with RPV and Complera/Eviplera as small increases in serum creatinine have been observed in humans treated with RPV, likely due to inhibition of renal transporters for creatinine. However, these are not considered to be clinically important {22839}.

Renal Events

Across all studies of E/C/F/TAF, there were no cases of proximal renal tubulopathy (PRT) reported (including Fanconi syndrome) in HIV-infected subjects receiving E/C/F/TAF.
In Study GS-US-292-0109 in virologically suppressed subjects, 1 subject in the FTC/TDF+3rd Agent group (taking COBI-boosted atazanavir [ATV+COBI]+TVD) had a renal AE of Fanconi syndrome which resulted in discontinuation of study drug.

Renal Laboratory Parameters

*E/C/F/TAF Studies*

As expected due to the inhibitory effect of COBI on renal tubular secretion of creatinine, increases in serum creatinine were seen after initiation of E/C/F/TAF in ART-naive subjects. The magnitude of these increases was similar to those noted after initiation of treatment with regimens including RTV and RPV, which also have this effect {25886}, {18038}, {19105}, {28739}.

Across all E/C/F/TAF ART-naive studies, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. A consistent effect on serum creatinine was observed in ART-naive adults and adolescents receiving E/C/F/TAF (mean [SD] increase from baseline: ART-naive adults 0.08 [0.124] mg/dL at Week 48; ART-naive adolescents 0.10 [0.083] mg/dL at Week 24). Increases were observed by Week 2 and remained stable. Across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, minimal changes in serum creatinine were observed in subjects receiving E/C/F/TAF. At Week 48 in Study GS-US-292-0109, the mean (SD) changes from baseline in serum creatinine were as follows: E/C/F/TAF −0.01 (0.117) mg/dL; FTC/TDF+3rd Agent 0.04 (0.123) mg/dL ($p < 0.001$ for the difference between groups). In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, the mean (SD) increase in serum creatinine was 0.05 (0.28) mg/ dL.

Across all E/C/F/TAF ART-naive studies, fewer subjects receiving E/C/F/TAF developed treatment-emergent proteinuria than subjects receiving STB. Across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, statistically significant decreases in proteinuria were observed. In the ART-naive Phase 3 studies, significantly less proteinuria,

quantified by urine protein to creatinine ratio (UPCR), and a decrease from baseline in albuminuria, quantified by urine albumin to creatinine ratio (UACR), in the E/C/F/TAF group were observed at Week 2 and persisted through Week 48. In contrast, there was an increase from baseline in UPCR and UACR in the STB group. Across studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, decreases in proteinuria, quantified by UPCR, and decreases in albuminuria, quantified by UACR, were observed as early as Week 1 and persisted through Week 48. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% to 21% and 49% to 27%, respectively, through Week 24. In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, median percentage changes from baseline in UPCR and UACR were 0.1% and −19.5%, respectively.

Across the E/C/F/TAF ART-naive studies, there was minimal change from baseline in RBP to creatinine ratio for the E/C/F/TAF group and a progressive increase from baseline to Week 48 for the STB group. Across studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, decreases from baseline in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed as early as Week 1 and persisted through Week 48. Each of these differences between treatment groups was statistically significant favoring E/C/F/TAF.
In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, decreases from baseline in RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed at Week 24.

In the E/C/F/TAF ART-naive Phase 3 studies, there was no change from baseline in median (Q1, Q3) fractional excretion of uric acid (FEUA; marker of proximal renal tubular function) using adjusted serum creatinine at Week 48 in the E/C/F/TAF group, compared with an increase in the STB group (E/C/F/TAF 0.0% [−1.3%, 1.1%]; STB 0.4% [−0.8%, 2.0%]).

In E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109, subclinical renal tubulopathy was defined as confirmed abnormalities in any 2 out of 4 renal parameters (serum creatinine and 3 markers of tubular dysfunction). There were no cases identified with confirmed increases in serum creatinine plus confirmed increases in 2 of the 3 markers of tubular dysfunction for clinical review in either treatment group in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 (randomized phase and open-label extension) or in subjects with renal impairment in Study GS-US-292-0112. In Study GS-US-292-0109 in virologically suppressed subjects, no subjects in the E/C/F/TAF group had subclinical renal tubulopathy, while 1 subject in the FTC/TDF+3rd Agent group (taking ATV+COBI+TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

*RPV Studies*

In the 2 RPV Phase 3 studies, mean increases from baseline in serum creatinine values were observed for RPV-treated subjects in the FTC/TDF subgroup (0.12 mg/dL at Week 96). In the control group, small mean increases from baseline were observed with a maximum mean increase from baseline at Week 96. Values for mean changes from baseline in $eGFR_{creat}$ are opposite to those for serum creatinine; a mean increase from baseline in serum creatinine values represents a mean decrease from baseline in $eGFR_{creat}$ values. The maximum mean decrease

from baseline was 14.0 mL/min/1.73m$^2$ at Week 96 in the FTC/TDF subgroup. In the control group, similar to the pattern of mean change from baseline observed for the overall population, mean $eGFR_{creat}$ values fluctuated around baseline until Week 48 and then gradually decreased to Week 96 in the FTC/TDF subgroup.

In the RPV Phase 2b Study C213 in adolescents, mean increases from baseline in creatinine were observed at all time points in the 48-week treatment period. A maximum mean (SE) increase from baseline of 16.3 (13.49) µmol/L was observed at Week 1. At Week 48, a mean (SE) increase from baseline of 6.6 (1.39) µmol/L was observed. Note that the mean (SE) increase from baseline of 16.3 (13.49) µmol/L observed at Week 1 was due to a grade 4 creatinine increased value for one subject. Mean decreases from baseline in glomerular filtration rate (GFR) were observed at all time points in the 48-week treatment period. From Week 4 up to Week 24, mean (SE) decreases from baseline fluctuated between -0.18 (0.061) and -0.20 (0.058) mL/s/1.73m2, followed by a greater mean decrease from baseline at Week 32 of -0.34 (0.062) mL/s/1.73m2 which plateaued up to Week 48. At Week 48, a mean (SE) decrease from baseline of -0.32 (0.066) mL/s/1.73m2 was observed.

The pattern of these clinical observations for RPV is similar to that observed with cimetidine, where small increases of serum creatinine reflect a direct effect on the tubular secretion of creatinine rather than a true change in renal function. Estimated glomerular filtration rate for cystatin C ($eGFR_{cyst}$) values, as a marker of glomerular filtration, showed no mean decrease but rather a small mean increase from baseline in the RPV group. This clinical observation confirmed that RPV may interfere with the tubular secretion of creatinine, but has no effect on the actual glomerular filtration. Hence, mean changes from baseline in serum creatinine and $eGFR_{creat}$ values in the RPV group are not considered clinically relevant and are not indicative of RPV-induced nephrotoxicity.

*Complera/Eviplera Studies*

In Complera/Eviplera Studies GS-US-264-0106 and GS-US-264-0111, serum creatinine elevations were evident by Week 4 and stable through Week 24 and Week 48, respectively (mean [SD] increase from baseline at Weeks 4, 24, and 48 were 0.04 [0.107] mg/dL, 0.05 [0.119] mg/dL, and 0.05 [0.115] in Study GS-US-264-0106 and 0.07 [0.09] mg/dL, 0.12 [0.114] mg/dL, and 0.08 [0.119] mg/dL in Study GS-US-264-0111). None of the subjects had eGFR (MDRD) values indicative of stage 4 (severe) or stage 5 (renal failure) kidney disease at any time during the studies.

There were no clinically relevant changes from baseline in renal laboratory parameters following treatment with FTC/RPV/TAF in the Phase 1 studies.

### *Ocular Safety*

Posterior uveitis was observed in a nonclinical study with dogs treated at high dose of TAF, which was at 3.7- and 17-fold higher exposure to TAF and TFV, respectively, than that observed in human subjects administered a 25-mg dose. Therefore, in the E/C/F/TAF clinical program, analyses were conducted to evaluate the system organ class (SOC) term eye disorders to detect AEs where the symptoms reported may potentially represent posterior uveitis.

Specific ocular toxicity monitoring was not included in the studies of FTC, RPV, or FTC/RPV/TDF. Therefore, ocular safety data are presented below only for TAF-containing regimens.

Across all E/C/F/TAF studies, eye disorders were uncommon, balanced between treatment groups, and considered by the investigator as unrelated to the study drugs. For subjects who received E/C/F/TAF, no AEs in the eye disorders SOC were indicative of posterior uveitis, and only 1 subject discontinued study drugs due to 3 eye disorder AEs, all of which were considered related to study drugs by the investigator. One subject in Study GS-US-292-0106 had an AE of intermediate uveitis that was considered related to study drug by the investigator but was resolving while the subject continued on study drug without interruption. No subjects in the ophthalmic substudy of Study GS-US-292-0109 had fundoscopic findings consistent with uveitis.

***Cardiovascular Safety***

Supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram (ECG). There is no evidence of cardiac conduction abnormalities in studies with E/C/F/TAF to date.

TAF Studies

TAF, administered at doses of 25 and 125 mg, did not lead to changes in the QTc interval in healthy adults.

RPV Studies

Overall, the incidence of events of interest potentially related to QT interval prolongation was low and reported with similar grades in the pooled Phase 3 trials. Too few events of interest potentially related to QT interval prolongation were reported for meaningful conclusions to be drawn concerning the time to onset and duration of these events.

Phase 3 ECG data recorded while a subject was using concomitant medication with potential impact on QT were pooled for subgroup analysis. The mean maximum change from baseline in QTcF in the overall population was +21.6 ms in the rilpivirine group and +22.5 ms in the control group. In the rilpivirine group, the mean maximum change from baseline was similar in the subjects taking cytochrome (CYP)3A4 inhibitors by co medication with a potential impact on QT interval. The number of subjects taking a potassium depleting diuretic or a drug with known potential QT prolonging effect was too small (10 subjects or fewer) to draw valid conclusions.

Robust ECG monitoring in Phase 3 trials showed that there was a gradual increase over time in the mean QTcF in the rilpivirine group and the control group, with no gender difference. This increase was less pronounced in the TDF/FTC subgroup than in the zidovudine/ lamivudine (AZT/3TC) subgroup. In the pooled Phase 3 trials, the incidence of a prolonged QTcF (> 480 ms) was low with rilpivirine (0.3%) and with control (0.3%), with no gender or race differences. There were no QTcF increases > 500 ms, a typical proarrhythmic threshold. No AEs suggestive of ventricular tachyarrhythmia were reported. There was no relationship between exposure to

rilpivirine (area under the plasma concentration-time curve from time of intake up to 24 hours after dosing [AUC24h]) and the mean maximum change from baseline in QTcF. Therefore, in clinical practice it is not warranted to routinely exclude subjects using a concomitant medication with potential impact on QT from rilpivirine-based ART.

Across the Phase 3 trials there were no major changes in ECG parameters.

***Thyroid Safety***

Effects on the thyroid gland were noted in pre-clinical studies of E/C/F/TAF in rats, characterized by increased organ weight, hypertrophy of follicular epithelium, and reduced serum concentrations of T4. The effects occurred similarly in males and females and were noticed after 7 days of treatment. Upon longer duration of treatment, increased serum concentrations of TSH were recorded and also a differential effect on T3. TSH, T3, and T4 were assessed in the Phase 2 E/C/F/TAF Study GS-US-292-0102. No clinically relevant changes from baseline were observed for all 3 parameters, subsequently TSH, T3, and T4 were not assessed in the Phase 3 studies of E/C/F/TAF.

Thyroid toxicity has not been associated with treatment with RPV.

***Adrenal Safety***

Due to potential inhibition by rilpivirine of 17- and 21-hydroxylase in the adrenal gland, adrenal safety was evaluated in Phase 3 studies. Because specific adrenal toxicity monitoring was not included in the studies of FTC or TAF, adrenal safety data are presented below only for RPV studies.

The most commonly reported endocrine events of interest in the pooled Phase 3 trials at Week 96 on rilpivirine were in the SOC of investigations (3.8% in the rilpivirine group vs 1.9% in the control group) and were related to blood cortisol. Besides menorrhagia, the only endocrine event of interest reported in ≥1.0% of subjects in the rilpivirine group was decreased blood cortisol (2.9% in the rilpivirine group vs 1.6% in the control group). The incidence of these events was highest in the first 4 weeks for both treatment groups. After Week 4, endocrine events of interest were seen at a similar incidence and prevalence in both treatment groups throughout the 96 week treatment period.

The incidence of an abnormal cortisol response to adrenocorticotropic hormone (ACTH) stimulation was higher in the rilpivirine group than the control group over the 96-week treatment period (8.4% vs 3.4%, respectively). For the rilpivirine group, 4.2% of subjects did not reach the lower threshold of 450 nmol/L compared to 1.8% in the control group. The incidence of at least 2 consecutive abnormal cortisol responses (< 500 nmol/L) to ACTH stimulation was 2.3% in the rilpivirine group compared to 0.4% (2 subjects) in the control group. No endocrine events were reported as SAEs. No subjects discontinued the trial due to an AE of decreased blood cortisol (nor for any other endocrine event of interest). No grade 3 and 4 endocrine AEs were reported. There were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction in adults.

### *Skin and Subcutaneous Tissue Disorders*

Severe skin reactions have been reported during postapproval use of Complera/Eviplera.

In the pooled Phase 3 trials, skin events of interest were reported at a lower incidence and with lower grades in the rilpivirine group than in the control group. The greatest differences between the treatment groups in the incidence of AEs leading to discontinuation were observed in the SOC of skin and subcutaneous tissue disorders (0.3% on rilpivirine vs 1.8% on control), mostly driven by the individual preferred term (PT) rash. The incidence of rash showed no gender difference.

The incidence of rash (grouped term) was highest in the first 4 weeks, with a lower incidence in the rilpivirine group (4.2%) than the control group (15.1%). Few new rash events occurred thereafter, and with comparable incidence in the rilpivirine and control groups. More rash events led to permanent discontinuation in the control group than with rilpivirine and the rest mostly resolved. Therefore, the prevalence in the control group decreased after the first 4 weeks, but remained somewhat higher than with rilpivirine.

No cases of erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) have been reported during clinical development of rilpivirine.

### *Nervous System Disorders*

Nervous system symptoms, including dizziness, are a known side effect of EFV {33968}, {33005}, the comparator in RPV Studies C209 and C215, therefore were evaluated as events of interest. Nervous system disorders are not of special interest to FTC or TAF.

There were 195 subjects [28.4%] in the RPV group and 318 subjects [46.6%] in the control group reported with neurologic events of interest in the Week 96 pooled analysis. The most commonly reported neurologic events of interest on RPV were headache (15.5% in the RPV group vs 14.1% in the control group), dizziness (10.2% vs 29.6%, respectively), and somnolence (4.4% vs 7.5%, respectively). All other neurologic events of interest were reported in ≤ 1.5% of subjects in the RPV group.

### *Psychiatric Disorders*

Depression is an important identified risk for RPV and the RPV component of Complera/Eviplera.

In the Phase 3 Week 96 pooled analysis, 4.1% of subjects with EDURANT treatment were reported with the adverse drug reaction (ADR) depression of at least Grade 2. Grade 3 or 4 depression was seen in 0.7% of subjects treated with EDURANT and 0.7% of controls.

### *Hepatobiliary Disorders*

Hepatotoxicity was a key safety finding from nonclinical studies of RPV and was evaluated in clinical studies.

In the Phase 3 Week 96 pooled analysis, graded hepatic events of interest were reported at a similar incidence in both treatment groups. The incidence of hepatic events of interest was low in both treatment groups, with the highest incidence seen in the first 4 weeks of treatment. The prevalence of hepatic events of interest was constant over time. Hepatic events of interest were seen at a similar incidence and prevalence in both treatment groups.

The most commonly reported hepatic events of interest in the rilpivirine group were aspartate aminotransferase (AST) increased (2.5% versus [vs] 3.2% in the control group) and alanine aminotransferase (ALT) increased (2.0% vs 3.7% in the control group). All other hepatic events of interest were reported in ≤ 1.0% of subjects in either treatment group. The most common Grade 3 and 4 laboratory abnormalities in the rilpivirine group included AST increased (2.3% vs 3.2% in the control group), and ALT increased (1.6% vs 3.7% in the control group). Grade 4 laboratory abnormalities in the rilpivirine group included AST increased in 4 subjects (0.6%) and ALT increased in 6 subjects (0.9%).

Most individual AST and ALT abnormalities in rilpivirine -treated subjects were Grade 1 or 2 (i.e., mild or moderate) in severity in the pooled Phase 3 trials, and their incidence was not higher than in the control group. Mean decreases from baseline in ALT and AST were observed in both treatment groups throughout the 96-week treatment period. At Week 96, the mean decreases from baseline in ALT and AST values were 3.6 U/L and 4.4 U/L, respectively in the rilpivirine group and 6.4 U/L and 6.3 U/L, respectively in the control group.

**Clinical Laboratory Evaluations**

***Laboratory Abnormalities***

In all ART-naive Phase 3 studies included in this submission, there were no clinically relevant changes from baseline within groups or differences between the treatment groups in median values for hematology or clinical chemistry parameters; all median values were within normal ranges.

***Fasting Glucose and Lipid Parameters***

E/C/F/TAF Studies

For ART-naive and virologically suppressed subjects in the randomized studies of E/C/F/TAF, greater increases in the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol to HDL ratio, and triglycerides were observed in subjects treated with E/C/F/TAF compared with those treated with a TDF comparator at both Weeks 24 and 48. Consistent with these results, greater percentages of subjects treated with E/C/F/TAF than those treated with a TDF comparator had categorical changes in the National Cholesterol Education Program (NCEP) ATP III lipid classifications from baseline. These small lipid categorical changes were consistent with data from other studies of abacavir (ABC), stavudine (d4T), and other non-TDF-based NRTIs in ART-naive patients {11417}. In the E/C/F/TAF studies, the majority of lipid abnormalities were Grade 1 or 2, and the percentage of subjects who received concomitant lipid modifying agents during the study was comparable between treatment groups. Similarly, in the single-group Study GS-US-292-0112,

median changes from baseline in metabolic laboratory parameters at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects who received TDF at baseline and, notably, a trend toward decrease in most parameters for subjects who did not receive TDF at baseline.

The differences in metabolic laboratory parameters observed between treatment with E/C/F/TAF compared with TDF-containing regimens (including STB) may be associated with the previously reported lipid lowering effect of TFV {27870}, {16173} and the markedly lower plasma concentrations of TFV associated with TAF relative to TDF.

RPV Studies

For the FTC/TDF subset in the RPV Phase 3 studies, mean decreases from baseline were observed for triglyceride and LDL cholesterol values over the 96-week treatment period in the RPV group, compared with mean increases from baseline in the control group. Mean increases were seen for TC in both groups compared to baseline; however, these increases were more pronounced in the control group. Mean increases in HDL-cholesterol were observed for both groups. In the RPV adolescent study C213, mean decreases from baseline in total cholesterol were observed up to Week 48. After an initial mean decrease from baseline at Week 8, mean HDL cholesterol increases from baseline were observed up to Week 48. Mean decreases from baseline in LDL cholesterol were observed at all time points in the 48-week treatment period. Mean decreases from baseline in triglycerides were observed throughout the 48-week treatment period.

Complera/Eviplera Studies

In the Complera/Eviplera Study GS-US-264-0111 in virologically suppressed subjects, significant decreases from baseline in fasting total cholesterol, direct LDL cholesterol, and fasting triglycerides were observed starting as early as Week 12 and continuing through Week 48. Similar changes were observed in Study GS-US-264-0106 through 24 weeks of treatment, and the ratio of total cholesterol/HDL cholesterol decreased to a greater extent through Week 24 among subjects in the randomized FTC/RPV/TDF group versus those maintaining their baseline PI/r + 2 NRTIs regimen (SBR group). Differences between these treatment groups for all 5 of these lipid parameters were statistically significant at Week 24 ($p < 0.001$). The mean reductions from baseline in lipid parameters observed at Week 24 in the FTC/RPV/TDF group were generally maintained through Week 48 of therapy. After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24, similar decreases in lipid parameters were observed in the Delayed Switch group over Weeks 24 to 48 of the study. In Study GS-US-264-0106, similar results were obtained in categorical analyses of lipid parameters using categories consistent with the NCEP recommendations and WHO criteria for fasting lipid parameters.

In summary, switching to the RPV-containing regimen FTC/RPV/TDF, resulted in improvements in fasting lipids, including total cholesterol, direct LDL, triglycerides, and the ratio of total cholesterol to HDL cholesterol as early as 12 weeks after initiating therapy, and this effect was maintained through up to 48 weeks of therapy. A greater decrease in HDL cholesterol levels from baseline to Week 24 was observed in the FTC/RPV/TDF single-tablet regimen (STR) group compared with the SBR group; however, no significant differences in the

distribution of subjects across the fasting HDL categories were observed at Weeks 12 and 24 between the FTC/RPV/TDF and SBR groups.

**Safety in Special Groups and Situations**

The safety of FTC/RPV/TAF as assessed by reported AEs and laboratory test abnormalities associated with treatment with E/C/F/TAF and RPV+FTC/TDF, were not affected by sex, age, race, HIV-1 RNA level, CD4 count, prior treatment regimen, or region. Subgroup analyses of safety were based on the Phase 3 studies only.

***Safety in Subjects with Renal Impairment***

Pharmacokinetic (PK) and relevant safety data support administration of FTC/RPV/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min).

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies of E/C/F/TAF in healthy and HIV-infected subjects, baseline eGFR was not a statistically significant or clinically relevant covariate influencing TAF PK. As expected due to renal elimination, FTC PK parameters were higher in subjects with mild to moderate renal impairment compared with those having normal renal function in the Phase 2 and 3 E/C/F/TAF studies in ART naive subjects. However, the FTC PK parameters were comparable to the mean FTC PK parameters achieved in subjects with mild renal impairment not requiring dose adjustment (mean [%CV] AUC 19,900 [6.2] ng*h/mL; $C_{max}$ 3800 [2.3] ng/mL) {23270}, {30162}. Moreover, subjects with $eGFR_{CG} < 50$ mL/min did not have a different safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min. In view of the negligible renal excretion of TMC278 (C119), a trial to investigate the exposure to TMC278 in subjects with renal impairment has not been conducted. In view of the negligible renal excretion of TMC278 (< 1%), no dose adjustment of RPV is required in patients with renal impairment.

No additional measures outside of standard clinical practice guidelines for routine monitoring renal safety in subjects with mild to moderate renal impairment are indicated.

***Safety in Subjects with Hepatic Impairment***

Pharmacokinetic and relevant safety data support administration of FTC/RPV/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class A or B).

The PK of FTC/RPV/TAF has not been studied in subjects with hepatic impairment. The efficacy and safety of FTC/RPV/TAF have not been established in patients with significant underlying liver disorders. The PK of TAF and its metabolite TFV have been studied in subjects with moderate hepatic impairment, and no dose adjustment is required in these patients. The PK of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so no dose adjustment is anticipated in patients with mild to moderate hepatic impairment. Pharmacokintic data suggest that no dose adjustment of

TMC278 is needed in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the exposure to TMC278 has not been studied.

**Postmarketing Data**

As FTC/RPV/TAF has not been approved, no postmarketing data are available. Relevant postmarketing data for Complera/Eviplera are presented.

Since the data lock of the last Complera/Eviplera Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) on 10 February 2015, 2 postmarketing ADRs for Complera/Eviplera have been identified:

- Severe skin and hypersensitivity reactions
- Weight gain

Neither of these ADRs could be attributed to an individual component of Complera/Eviplera, given that they were identified in patients receiving the Complera/Eviplera FDC. They have, therefore, been described as ADRs to Complera/Eviplera in the company core data sheet (CCDS) and are also considered relevant for FTC/RPV/TAF.

# 1. EXPOSURE TO THE DRUG

## 1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

### 1.1.1. Primary Safety Populations for FTC/RPV/TAF

The safety of the FTC/RPV/TAF (200/25/25 mg) FDC is based on the established safety of E/C/F/TAF (150/150/200/10 mg), Edurant (RPV 25 mg), and Complera/Eviplera (FTC/RPV/TDF 200/25/300 mg) using a pharmacokinetic bioequivalence bridge between FTC/RPV/TAF and E/C/F/TAF (for the FTC/TAF component) and between FTC/RPV/TAF and Edurant (for the RPV component). The safety of E/C/F/TAF, Edurant, and Complera/Eviplera has been established in the following HIV-infected patient populations:

- Antiretroviral therapy (ART)-naive subjects: E/C/F/TAF pivotal Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 and the randomized phase of Phase 2 Study GS-US-292-0102; RPV pivotal Phase 3 Studies C209 and C215

- Virologically suppressed subjects: E/C/F/TAF Phase 3 Study GS-US-292-0109 and the open-label extension phase of Phase 2 Study GS-US-292-0102; Complera/Eviplera Phase 2b Study GS-US-264-0111 and Phase 3b Study GS-US-264-0106

- Subjects with mild to moderate renal impairment: E/C/F/TAF Phase 3 Study GS-US-292-0112

- ART-naive adolescent subjects: E/C/F/TAF Phase 2/3 Study GS-US-292-0106; RPV Phase 2 Study C213

Safety data from E/C/F/TAF studies were included in the E/C/F/TAF marketing application, which is currently under review. Safety data from Edurant and Complera/Eviplera were reviewed as part of approved marketing applications to support the use of RPV in combination with other ARVs for the treatment of HIV-1 infection across these multiple patient populations.

The principal sources of safety data for the FTC/RPV/TAF FDC are presented in Table 1.

**Table 1. Studies Supporting Clinical Safety for the FTC/RPV/TAF Fixed-Dose Combination Marketing Application**

| Study | Study Design | Number of Subjectsa by Treatment Regimen | Data Presented | CSR Reference and Narrative Locations |
|---|---|---|---|---|
| **E/C/F/TAF Studies** | | | | |
| **HIV-Infected, ART-Naive Adult Subjects** | | | | |
| GS-US-292-0104 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB | E/C/F/TAF FDC + placebo-to-match STB (N = 435)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 432) | Week 48 efficacy, PK, and safety | **CSR**: GS-US-292-0104 Week 48 CSR<br>**Narrative**: m2.7.3, Section 2.1.1.1 |
| GS-US-292-0111 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB | E/C/F/TAF FDC + placebo-to-match STB (N = 431)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 435) | Week 48 efficacy, PK, and safety | **CSR**: GS-US-292-0111 Week 48 CSR<br>**Narrative**: m2.7.3, Section 2.1.1.2 |
| GS-US-292-0102 | Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB<br>Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in the D/C/F/TAF Phase 2 Study GS-US-299-0102 | Randomized phase:<br>E/C/F/TAF FDC + placebo-to-match STB (N = 112)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 58)<br>Open-label extension phase:<br>Continued on E/C/F/TAF FDC (N = 105)<br>Switch to E/C/F/TAF FDC (N = 161)<br>from STB to E/C/F/TAF (N = 53)<br>from D/C/F/TAF to E/C/F/TAF (N = 70)<br>from DRV+COBI+TVD to E/C/F/TAF (N = 38) | Week 48b efficacy, PK, and safety | **CSR**: GS-US-292-0102 Week 96 CSR<br>**Narrative**: m2.7.3, Section 2.1.1.3 |

| Study | Study Design | Number of Subjectsa by Treatment Regimen | Data Presented | CSR Reference and Narrative Locations |
|---|---|---|---|---|
| **HIV-Infected, Virologically Suppressed Adult Subjects** | | | | |
| GS-US-292-0109 | Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to E/C/F/TAF FDC | Switch to E/C/F/TAF FDC (N = 959)<br>Stay on FTC/TDF+3rd Agent (N = 477) | Week 48 efficacy and safety | **CSR**: GS-US-292-0109 Week 48 CSR<br>**Narrative**: m2.7.3, Section 2.1.2.1 |
| **HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment** | | | | |
| GS-US-292-0112 | Phase 3, open-label, multicenter, multiple cohort study evaluated the safety, efficacy, and tolerability of E/C/F/TAF FDC | E/C/F/TAF FDC (N = 248) | Week 24 efficacy and safety | **CSR**: GS-US-292-0112 Week 24 CSR<br>**Narrative**: Section 1.1.4.1.1 |
| **HIV-Infected, ART-Naive Adolescent Subjects** | | | | |
| GS-US-292-0106 | Phase 2/3, open-label, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC | E/C/F/TAF FDC (N = 48)<br>PK substudy: N = 24 | Week 24 efficacy, PK, and safety | **CSR**: GS-US-292-0106 Week 24 CSR<br>**Narrative**: Section 1.1.4.1.2 |

| Study | Study Design | Number of Subjectsa by Treatment Regimen | Data Presented | CSR Reference and Narrative Locations |
|---|---|---|---|---|
| **RPV Studies** | | | | |
| **HIV-Infected, ART-Naive Adult Subjects** | | | | |
| TMC278-TiDP6-C209 (C209, ECHO) | Randomized, double-blind, double-dummy, active-controlled international trial to assess the long-term efficacy, safety, and tolerability of RPV compared to EFV, each in combination with a fixed background N(t)RTI regimen containing TDF and FTC, in HIV-1 infected, ARV treatment-naive subjects.<br>After the 96-week double-blind treatment period all subjects could enter a post 96-week double-blind extension until Week 96 database lock. After the Week 96 database lock all subjects could enter an open-label continued access extension until the final visit (for EFV-treated subjects and RPV-treated subjects not rolling-over into another trial) or until the roll-over visit (for other RPV-treated subjects). | RPV 25 mg taken once daily (n = 346) + background N(t)RTI regimen (RPV + FTC/TDF = 346)<br>Or<br>EFV 600 mg taken once daily (n = 344) + background N(t)RTI regimen for 96 weeks (EFV + FTC/TDF = 344) | Week 48 and 96 efficacy and safety | **CSR**: m2.7.3, Appendix 7.1.2<br>**Narrative**: m2.7.3, Section 2.2.1.1 |

| Study | Study Design | Number of Subjectsa by Treatment Regimen | Data Presented | CSR Reference and Narrative Locations |
|---|---|---|---|---|
| TMC278-TiDP6-C215 (C215, THRIVE) | Randomized, double-blind, double-dummy, active-controlled international trial to compare the long-term efficacy, safety, and tolerability of RPV vs EFV, each in combination with a background N(t)RTI regimen containing 2 N(t)RTIs in HIV-1 infected, ARV treatment-naive subjects. The investigator-selected N(t)RTIs were either ABC/3TC, AZT/3TC, or FTC/TDF.<br>After the 96-week double-blind treatment period all subjects could enter a post 96-week double-blind extension until Week 96 database lock. After the Week 96 database lock all subjects could enter an open-label continued access extension until the final visit (for EFV-treated subjects and RPV-treated subjects not rolling-over into another trial) or until the roll-over visit (for other RPV-treated subjects). | RPV 25 mg taken once daily (n = 340) + background N(t)RTI regimen (RPV + FTC/TDF = 204)<br>Or<br>EFV 600 mg taken once daily (n = 338) + background N(t)RTI regimen for 96 weeks (EFV + FTC/TDF = 202) | Week 48 and Week 96 efficacy and safety | **CSR**: m2.7.3, Appendix 7.1.2<br>**Narrative**: m2.7.3, Section 2.2.1.2 |
| **HIV-Infected, ART-Naive Adolescent Subjects** | | | | |
| TMC278-TiDP38-C213 (C213, PAINT) | Phase 2, open-label, single arm trial to evaluate the PK, safety, tolerability, and antiviral activity of RPV in antiretroviral-naive HIV-1 infected adolescents aged 12 to < 18 years. | RPV + investigator-selected background regimen of 2 N(t)RTIs (N = 36) | Week 48 efficacy, PK, and safety | **CSR**: TMC278-C213-W48-CSR<br>**Narrative**: Section 1.1.4.2.1 |

| Study | Study Design | Number of Subjectsa by Treatment Regimen | Data Presented | CSR Reference and Narrative Locations |
|---|---|---|---|---|
| **Complera/Eviplera Studies** | | | | |
| **HIV-Infected, Virologically Suppressed Adult Subjects** | | | | |
| GS-US-264-0111 | Phase 2b, open-label, multicenter study to evaluate switching from EFV/FTC/TDF to FTC/RPV/TDF STR in virologically suppressed HIV-1 infected subjects on EFV/FTC/TDF desiring change in regimen due to EFV intolerance | FTC/RPV/TDF STR Group:<br>FTC 200 mg/RPV 25 mg/ TDF 300 mg STR taken orally once daily for 48 weeks<br>(N = 49) | Week 48 efficacy and safety | **CSR**: m2.7.3, Appendix 7.1.3<br>**Narrative**: m2.7.3, Section 2.3.1.1 |
| GS-US-264-0106 | Phase 3b, randomized, open-label, multicenter study to evaluate the safety and efficacy of switching from regimens consisting of a PI/r and 2 NRTIs to FTC/RPV/TDF STR in virologically suppressed, HIV-1 infected subjects | FTC/RPV/TDF STR Group:<br>FTC 200 mg/RPV 25 mg/ TDF 300 mg STR taken orally once daily for 48 weeks (N = 317)<br>Stay on Baseline Regimen (SBR) Group:<br>Remain on baseline regimen for 24 weeks, then switch to FTC/RPV/TDF STR for 24 weeks<br>(N = 159)<br>Delayed Switch Group:<br>Subjects in the SBR group who switched to FTC/RPV/TDF after 24 weeks on their baseline regimen (N = 152)<br>Total FTC/RPV/TDF Group:<br>FTC/RPV/TDF STR group + Delayed Switch group<br>(N = 469) | Week 48 efficacy and safety | **CSR**: m2.7.3, Appendix 7.1.3<br>**Narrative**: m2.7.3, Section 2.3.1.2 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b Most subjects in the randomized phase of Study GS-US-292-0102 received study drug for ≥ 60 weeks when unblinding occurred; most subjects in the open-label extension had completed ≥ 24 weeks of treatment.E/C/F/TAF Studies

### ART-Naive Adult Subjects

The 2 pivotal Phase 3 E/C/F/TAF studies supporting the safety of the concurrent administration of FTC and TAF for the treatment of HIV-1 infection in ART-naive subjects are Studies GS-US-292-0104 and GS-US-292-0111, which were randomized, double-blind studies that used STB as the comparator (m2.7.3, Sections 2.1.1.1 and 2.1.1.2 for summary information). Eligible subjects were ART-naive (excluding pre-exposure prophylaxis or postexposure prophylaxis up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA ≥ 1000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 50 mL/min at screening. Data are presented through a data cutoff performed when all randomized subjects had completed the Week 48 visit or had discontinued study drugs before their Week 48 visit.

The data from Studies GS-US-292-0104 and GS-US-292-0111 are supported by the Phase 2, randomized, double-blind, active-controlled Study GS-US-292-0102 (randomized phase), which evaluated E/C/F/TAF versus STB in ART-naive, HIV-infected adult subjects (m2.7.3, Section 2.1.1.3 for summary information). Eligible subjects for the randomized phase of the study had plasma HIV-1 RNA levels ≥ 5000 copies/mL, no prior use of any approved or experimental anti-HIV drug for any length of time, and an $eGFR_{CG}$ ≥ 70 mL/min at screening. The randomized phase of the study was 48 weeks. Data are presented through a data cutoff performed when all subjects enrolled into the randomized phase had completed 96 weeks of study drug treatment, or had discontinued study treatment before their Week 96 visit.

Using STB as a comparator in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 allows for a direct comparison of the safety of TAF versus TDF, as the other components of the regimen and their respective doses are identical (ie, EVG 150 mg, COBI 150 mg, and FTC 200 mg).

### Virologically Suppressed Adult Subjects

Data from Study GS-US-292-0109 support the safety of E/C/F/TAF in virologically suppressed subjects who switched to E/C/F/TAF from regimens containing FTC/TDF (m2.7.3, Section 2.1.2.1 for summary information). All subjects in this Phase 3 open-label study were enrolled from a predefined set of Gilead clinical studies. Eligible subjects were HIV-infected adults receiving ART regimens consisting of STB, ATR, COBI-boosted atazanavir ([ATV+COBI])+TVD, or RTV-boosted ATV ([ATV+RTV])+TVD for at least 6 consecutive months preceding the final visit in their earlier study and who had maintained plasma HIV-1 RNA levels at undetectable levels for at least 6 consecutive months prior to the screening visit, had HIV-1 RNA < 50 copies/mL at the screening visit, and had an $eGFR_{CG}$ ≥ 50 mL/min at screening. Subjects must have completed between 60 and 144 weeks of treatment with another regimen in the previous study.

The choice of comparators in Study GS-US-292-0109 allowed evaluation of the safety of switching to E/C/F/TAF or remaining on a TDF-containing standard-of-care regimen.

The data cutoff for Study GS-US-292-0109 was performed when all subjects randomized by 31 October 2013 had been followed through the lower limit of Week 48 analysis window (ie, Week 42) or had discontinued study treatment before this time.

Data are also available from the extension phase of Study GS-US-292-0102, in which HIV-infected subjects who had previously received STB in the randomized phase and subjects who had received darunavir (DRV)/COBI/FTC/TAF (D/C/F/TAF) in Study GS-US-299-0102 were allowed to switch to open-label E/C/F/TAF.

**Adult Subjects with Mild to Moderate Renal Impairment**

The safety of E/C/F/TAF in adult subjects with mild to moderate renal impairment is supported by data from Study GS-US-292-0112, which was a Phase 3 open-label study that enrolled both ART-experienced (switch) and ART-naive subjects (summary information in Section 1.1.4.1.1). For the switch cohort (Cohort 1), eligible subjects were HIV-infected adults with plasma HIV-1 RNA concentrations at undetectable levels for at least 6 months and at < 50 copies/mL at screening, CD4 count ≥ 50 cells/μL, no history of known resistance to EVG, FTC, or TDF, and stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening. For the ART-naive cohort (Cohort 2), eligible subjects were HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count ≥ 50 cells/μL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening. The study planned to enroll a subset of at least 30 subjects (either switch or ART-naive) with screening $eGFR_{CG}$ of 30 to 49 mL/min.

The data cutoff was performed when all subjects who initiated study drugs on or prior to 15 November 2013 either completed their Week 48 study visits or prematurely discontinued study drugs before their Week 48 visits.

**ART-Naive Adolescent Subjects**

The safety of E/C/F/TAF in adolescent subjects is supported by data from the Phase 2/3 open-label Study GS-US-292-0106 (summary information in Section 1.1.4.1.2). Eligible subjects were HIV-infected, ART-naive adolescents of 12 to < 18 years of age weighing ≥ 35 kg, with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count > 100 cells/μL, and eGFR ≥ 90 mL/min/1.73m$^2$ (as calculated using the Schwartz formula) at screening, no prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission), and sensitivity to EVG, FTC, and TFV as demonstrated by HIV-1 genotyping at screening.

The interim Week 24 analysis for Study GS-US-292-0106 was conducted when all subjects enrolled in Parts A and B by 11 February 2014 (N = 23) had completed their Week 24 visit.

#### 1.1.1.1. RPV Studies

**ART-Naive Subjects**

The 2 investigational, double-blind, and active-controlled Phase 3 trials in HIV-1 infected, treatment-naive subjects, C209 (also known as ECHO) and C215 (also known as THRIVE), are the principal sources of safety information for RPV (m2.7.3, Sections 2.2.1.1 and 2.2.1.2 for summary information, respectively). Forty percent of subjects (550 of 1368) enrolled in the RPV Phase 3 trials received FTC/TDF with RPV (ie, are included in the FTC/TDF subset). For this marketing application, the FTC/TDF subset is presented because it provides data for RPV and FTC administered with a TFV prodrug and, therefore, contains the most relevant data for the FTC/RPV/TAF combination. The trials were conducted with TMC278 25 mg once daily versus efavirenz (EFV) 600 mg once daily, both in combination with a background regimen of 2 N(t)RTIs. For trial C209, randomization was stratified by screening viral load, and for trial C215, randomization was stratified by screening viral load and the selected ARV regimen. For both trials, data are presented from the Week 96 analysis; this analysis was performed when all subjects had completed at least 96 weeks of treatment or had discontinued earlier.

**ART-Naive Adolescent Subjects**

The current Summary of Clinical Safety presents an overview of the safety data of the Week 48 analysis of the Phase 2 study TMC278-TiDP38-C213 (referred to as C213; summary information in Section 1.1.4.2.1). C213 is an ongoing, open-label, Phase 2 study conducted at multiple sites to evaluate the PK, safety/tolerability, and efficacy of RPV 25 mg qd in combination with an investigator-selected background regimen containing 2 NRTIs in ARV treatment-naive, HIV-1 infected adolescents aged ≥12 to <18 years and weighing ≥32 kg. The primary efficacy endpoint was at Week 24. In addition, safety/tolerability, efficacy and PK of RPV were evaluated over a 48-week treatment period. Subjects who experienced and were expected to continue experiencing clinical benefit from RPV and their background regimen comprising 2 NRTIs at the end of the initial 48-week treatment period, had the option to continue their ARV treatment through this study for an additional 4 years in a post Week 48 treatment extension period. During this extension period, safety and efficacy of RPV will be evaluated.

This Summary of Clinical Safety presents a summary of the results of the Week 48 analysis of this study, which was performed when all subjects had completed at least 48 weeks of treatment or discontinued earlier (cut-off date 12 June 2014).

#### 1.1.1.2. Complera/Eviplera Studies

**Virologically Suppressed Adult Subjects**

The present submission provides data from 2 studies of Complera/Eviplera in ARV virologically suppressed subjects, Study GS-US-264-0111 and Study GS-US-264-0106 (m2.7.3, Section 2.3.1.1 and 2.3.1.2 for summary information, respectively).

Study GS-US-264-0111 was a Phase 2b open-label study that enrolled virologically suppressed (HIV-1 RNA < 50 copies/mL), HIV-1 infected subjects who had received ATR for at least

3 months and wished to switch to an alternate, potentially better tolerated regimen. Subjects switched from EFV/FTC/TDF single-tablet regimen (STR) to FTC/RPV/TDF STR. Safety data through Week 48 have been analyzed; results are summarized in this Summary of Clinical Safety and are fully described in the associated clinical study report (CSR).

Study GS-US-264-0106 was a Phase 3b open-label, noninferiority study that evaluated switching to FTC/RPV/TDF relative to staying on regimens consisting of 2 nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI/r) in order to further elucidate the outcomes of switching to the STR. In this study, adult subjects who were virologically suppressed (HIV-1 RNA < 50 copies/mL) while receiving 2 NRTIs + PI/r were randomized to receive FTC/RPV/TDF once daily or to stay on their baseline regimen (SBR) through Week 24 of the study. After 24 weeks, those randomized to stay on their baseline regimen switched to FTC/RPV/TDF for 24 weeks, while the group originally randomized to FTC/RPV/TDF remained on that regimen for an additional 24 weeks. Safety data from GS-US-264-0106 through Week 48 have been analyzed; results are summarized in this Summary of Clinical Safety and are fully described in the associated CSR.

### 1.1.2. Other Safety Populations Supportive of FTC/RPV/TAF

Supportive safety data are also provided by Phase 1 studies (including FTC/RPV/TAF, E/C/F/TAF, F/TAF, and TAF) that showed TAF was safe and generally well tolerated in healthy subjects. Deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs) are summarized for the FTC/RPV/TAF, TAF, F/TAF, and E/C/F/TAF Phase 1 studies. Further details on these Phase 1 studies are provided in the individual CSRs located as specified in Table 2.

Phase 2 and 3 studies for FTC are also included with this application as supportive safety information, listed in Table 3.

**Table 2. Phase 1 Studies Providing Supporting Clinical Safety for the FTC/RPV/TAF Fixed-Dose Combination**

| Safety Population | Studies Included in Population | N Receiving TAF | CSR Reference |
|---|---|---|---|
| FTC/RPV/TAF | GS-US-366-1159 (BE) | 96[a] | GS-US-366-1159 Final CSR |
| | GS-US-366-1651 (food effect) | 60 | GS-US-366-1651 Final CSR |
| | GS-US-366-1689 (DDI) | 42 | GS-US-366-1689 Final CSR |
| E/C/F/TAF | GS-US-292-0101 (dose ranging) | 38 | GS-US-292-0101 Final CSR |
| | GS-US-292-0103 (BE) | 34 | GS-US-292-0103 Final CSR |
| | GS-US-292-0108 (race/ethnicity) | 20 | GS-US-292-0108 Final CSR |
| F/TAF | GS-US-311-0101 (DDI) | 50 | GS-US-311-0101 Final CSR |
| TAF | GS-120-1101 (first in human) | 20 | GS-120-1101 Final CSR |
| | GS-US-120-0104 (dose ranging) | 25 | GS-US-120-0104 Final CSR |
| | GS-US-120-0107 (tQT) | 58 | GS-US-120-0107 Final CSR |
| | GS-US-120-0108 (renal impairment) | 27 | GS-US-120-0108 Final CSR |
| | GS-US-120-0109 (ADME) | 8 | GS-US-120-0109 Final CSR |
| | GS-US-120-0114 (hepatic impairment) | 40 | GS-US-120-0114 Final CSR |

a 1 subject discontinued the study after only receiving treatment C (E/C/F/TAF) so did not receive FTC/RPV/TAF

**Table 3. Other FTC Studies**

| Safety Population | Studies Included in Population | Location |
|---|---|---|
| FTC Phase 2 and Phase 3 | FTC-301A | Appendix 8.1.4 |
| | FTC-302 | |
| | FTC-303 | |
| | FTC-203 | |

### 1.1.3. Safety Assessments and Statistical Analysis Methods

Primary safety data were pooled for the 2 pivotal Phase 3 E/C/F/TAF studies (Studies GS-US-292-0104 and GS-US-292-0111) because the study designs and populations were identical, differing only in geography. Pooling of the individual Phase 3 RPV data for trials C209 and C215 was considered appropriate due to the similarity in the trials' designs. Key analyses for subjects receiving FTC/TDF in the RPV Phase 3 trials, including all subjects in C209 and a subset of subjects participating in trial C215, are presented in this document. For this marketing application, the FTC/TDF subset is presented for these studies because it provides data for RPV and FTC administered with a TFV prodrug and, therefore, contains the most relevant data for the FTC/RPV/TAF combination. For certain parameters (eg analysis of AEs by SOC, Section 2.1.9) FTC/TDF subset data are not available, in which case the overall pooled C209 and C215 data are presented.

Unless otherwise stated, no data from other studies were pooled due to differences in the subject populations studied, treatment durations, and randomization. For E/C/F/TAF studies, the primary safety data consist of 4 distinct subject populations: ART-naive adults, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescents. For RPV studies, the primary safety data consist of 2 distinct subject populations: ART-naive adults and ART-naive adolescents, and for Complera/Eviplera studies the primary safety data consist of virologically suppressed subjects. The main safety endpoint analysis was at 48 weeks for all studies except E/C/F/TAF Studies GS-US-292-0112 and GS-US-292-0106 (24 weeks), and RPV studies C209 and C215 (Week 96). All studies in ART-naive adults were double-blind, randomized studies, all other studies were open-label. Data for E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, as well as RPV trials C209 and C215, are presented pooled or side-by-side, respectively; data for other studies are presented individually.

Different coding systems and versions were used in classifying AEs collected across some clinical studies in this submission. For all E/C/F/TAF Phase 2, and Phase 3 studies described in this document, clinical and laboratory AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0, with SOC, high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) attached to the clinical databases. Reported AEs were classified using the MedDRA PTs and coded consistently within trials C209 and C215 using Version 11.0 of MedDRA for the Phase III pooled analysis. For RPV trial C213, AEs were coded in accordance with the MedDRA, Version 13.1, using the LLT as the description most closely related to the investigator's terminology, a PT describing a group of closely related LLTs, and the system organ class (SOC), which is the broad category including related PTs. For Complera/Eviplera studies, clinical and laboratory AEs were coded using the MedDRA, Version 15.

In this summary, all AEs discussed were treatment emergent and are referred to as AEs.

All AEs were assessed by the investigator or qualified designee and recorded on the AE electronic case report form (eCRF). The AE entry indicated whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug or to a study procedure, the action taken with the study drugs due to the AE, and

the severity of the AE. The investigator was responsible for final review and confirmation of accuracy of events, relationship, and severity, confirmed by the signature on the eCRF.

For the E/C/F/TAF studies and Complera/Eviplera Study GS-US-264-0111, laboratory abnormalities were not usually recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that required medical or surgical intervention or led to study drug interruption or discontinuation were recorded as an AE or SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram [ECG], x-rays, vital signs) associated with signs and/or symptoms were recorded as an AE or SAE if they met the definitions. If the laboratory abnormality was part of a syndrome, the syndrome or diagnosis was recorded (eg, anemia), not the laboratory result (eg, decreased hemoglobin).For the Phase 3 RPV studies, clinically relevant changes in laboratory values, other diagnostic tests (except for changes in plasma viral load, resistance pattern or HIV-related events), and intercurrent illnesses were recorded as AEs. For Complera/Eviplera Study GS-US-264-0106, an AE associated with laboratory abnormalities was recorded as an AE only if the investigator considered the laboratory abnormality clinically significant.

For the E/C/F/TAF studies, all AEs and laboratory abnormalities were recorded according to uniform guidelines and were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. For RPV studies, the severity of AEs and toxicity of laboratory and vital signs abnormalities were Division of Acquired Immunodeficiency Syndrome (DAIDS) graded. For Complera/Eviplera studies, AEs were graded for severity by investigators based on the Gilead modified National Institute of Allergy and Infectious Disease (NIAID) severity scale. Clinical laboratory abnormalities were graded by the central laboratory using the modified NIAID severity scale. For the statistical analyses, hyperglycemia and hypercalcemia were graded according to DAIDS grading scale instead of the NIAID severity scale. In addition, for urinalysis, hematuria (dipstick) was graded as follows in the statistical analyses: Grade 1 (1+), Grade 2 (2+), and Grade 3 (3–4+). Glycosuria (dipstick) was graded as follows: Grade 1 (1–2+), Grade 2 (3+), and Grade 3 (4+).

To control for the overall type I error in the assessment of the primary efficacy endpoint and the key safety endpoints in the E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109; hypothesis testing was performed in sequential order. The primary hypothesis of noninferiority of E/C/F/TAF relative to the active comparator in each study, with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the Food and Drug Administration [FDA] snapshot algorithm) was tested first. The noninferiority test was performed at a 1-sided, 0.02499 alpha level for Studies GS-US-292-0104 and GS-US-292-0111 and 0.02495 for Study GS-US-292-0109. If noninferiority was established, multiplicity adjustments were performed for the following safety endpoints with a fallback procedure in the sequential order given below, with prespecified 2-sided alpha levels {23531}:

A) Hip bone mass density (BMD) (alpha = 0.02)

B) Spine BMD (alpha = 0.01)

C) Serum creatinine (alpha = 0.01998 for Studies GS-US-292-0104 and GS-US-292-0111; 0.0199 for Study GS-US-292-0109)

D) Treatment-emergent proteinuria for Studies GS-US-292-0104 and GS-US-292-0111; EFV-related symptom assessment score for Study GS-US-292-0109 (alpha = 0.00)

Further details on the statistical methods, safety data definitions, and grading scales for E/C/F/TAF studies are provided in the E/C/F/TAF Integrated Summary of Safety statistical analysis plan (E/C/F/TAF ISS SAP) and are included in sections below when appropriate. The Phase 3 Week 96 pooled analysis is described in the TMC278-C904-W96-SAP. Further details on the statistical methods, safety data definitions, and grading scales for all studies are provided in the individual SAPs.

### 1.1.4. Summary of Results of Individual Studies

Narrative safety data from biopharmaceutic, clinical pharmacology, and efficacy studies of E/C/F/TAF, RPV, Complera/Eviplera, F/TAF, and TAF are presented in m2.7.1, m2.7.2, and m2.7.3.

#### 1.1.4.1. E/C/F/TAF Studies

Narrative safety data are provided in this section for subjects with mild to moderate renal impairment receiving E/C/F/TAF (GS-US-292-0112, Section 1.1.4.1.1) and for ART-naive adolescent subjects receiving E/C/F/TAF (GS-US-292-0106, Section 1.1.4.1.2).

##### 1.1.4.1.1. Subjects with Mild to Moderate Renal Impairment in Study GS-US-292-0112

A complete study description and results for Study GS-US-292-0112 are available in the CSR (GS-US-292-0112 Week 24 CSR), and a brief narrative of this study is presented below.

**Title of Study:** A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

**Objectives:** Study GS-US-292-0112 was conducted to evaluate safety, efficacy, and tolerability of E/C/F/TAF FDC in in HIV-infected adult subjects with stable, mild to moderate renal function (subjects with baseline $eGFR_{CG}$ 30 to 69 mL/min, inclusive).

The primary objective of this study was as follows:

- To evaluate the effect of the E/C/F/TAF FDC on renal parameters at Week 24

The secondary objectives of this study were as follows:

- To evaluate the effect of the E/C/F/TAF FDC on renal parameters at Weeks 48 and 96
- To measure the proportion of subjects achieving virologic response (HIV-1 RNA < 50 copies/mL, FDA snapshot algorithm) at Weeks 24, 48, and 96

- To evaluate the safety and tolerability of the E/C/F/TAF through 96 weeks of treatment

**Diagnosis and Main Criteria for Inclusion:**

**Cohort 1 (Switch):** Eligible subjects were HIV-infected adults with plasma HIV-1 RNA concentrations at undetectable levels for at least 6 months and < 50 copies/mL at screening, CD4+ cell count ≥ 50 cells/μL, no history of known resistance to EVG, FTC, or TDF, and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening.

**Cohort 2 (ART-Naive):** Eligible subjects were ART naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4+ cell count ≥ 50 cells/μL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening.

**SUMMARY OF RESULTS:**

**Subject Disposition and Demographics:** Of the 380 subjects screened, 252 were enrolled in the study (246 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects). A total of 248 subjects received at least 1 dose of study drug (242 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects).

Of the 248 treated subjects, 6.5% (16 subjects) discontinued study drug treatment, all of whom were Cohort 1 switch subjects. The reasons for discontinuation of study drug in the Cohort 1 switch subjects (n = 242) were AE (3.3%, 8 subjects), withdrew consent (1.2%, 3 subjects), lost to follow-up (0.8%, 2 subjects), lack of efficacy (0.4%, 1 subject), protocol violation (0.4%, 1 subject), and investigator's discretion (0.4%, 1 subject).

***Cohort 1: Switch Subjects***

The majority of subjects were male (79.3%), and the median age was 58 years (range: 24 to 82). A total of 63 subjects (26%) were ≥ 65 years of age. The most common races were white (62.8%), black (18.2%), or Asian (14.0%), and the most common ethnicity was not Hispanic/Latino (86.4%). The median (Q1, Q3) BMI at baseline was 24.1 (21.4, 26.9) $kg/m^2$.

Of 242 Cohort 1 switch subjects, 39.3% had a medical history of hypertension, and 13.6% had a medical history of diabetes. A total of 65.3% of subjects were taking TDF-containing regimens prior to switching to E/C/F/TAF. The baseline median (Q1, Q3) values for CD4 count and CD4% were 632 (456, 811) cells/μL and 34.7% (26.4%, 41.1%), respectively. Overall, 97.5% of subjects had baseline HIV-1 RNA < 50 copies/mL. The most common HIV risk factor categories were homosexual sex (52.1% of subjects) and heterosexual sex (40.9% of subjects). The majority of subjects (74.4%) had asymptomatic HIV-1 infection; 11.6% had symptomatic HIV-1 infection, and 14.0% were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ was 55.6 (45.7, 62.4) mL/min. Overall, 33.1% of subjects (80 of 242) had $eGFR_{CG}$ < 50 mL/min, 42.3% of subjects (101 of 239) had clinically significant proteinuria (UPCR > 200 mg/g), and 48.9% of subjects (115 of 235) had clinically significant albuminuria (UACR ≥ 30 mg/g). At baseline, 9.5% of subjects had Grade 2

proteinuria by urinalysis (dipstick), 23.1% of subjects had Grade 1 proteinuria. Most subjects were in chronic kidney disease (CKD) Stage 3 ($eGFR_{CG}$ 30 to 59 mL/min; 63.6%).

***Cohort 2: ART-Naive Subjects***

All 6 subjects were male, and the median age was 54 years (range: 46 to 65). The races were black (3 subjects), white (2 subjects), and Asian (1 subject), and the most common ethnicity was not Hispanic/Latino (5 subjects). The median (Q1, Q3) BMI at baseline was 23.6 (21.4, 25.7) $kg/m^2$.

The baseline median (Q1, Q3) values for HIV-1 RNA, CD4 count, and CD4% were 4.72 (4.01, 5.35) $log_{10}$ copies/mL, 397 (184, 673) cells/µL, and 24.6% (11.7%, 28.8%), respectively. Four subjects had baseline HIV-1 RNA ≥ 50 to ≤ 100,000 copies/mL, and 2 subjects had baseline HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL. The HIV risk factor categories were homosexual sex (3 subjects) and heterosexual sex (3 subjects). Five subjects had asymptomatic HIV-1 infection, and 1 subject had symptomatic HIV-1 infection.

The median (Q1, Q3) $eGFR_{CG}$ in Cohort 2 ART-naive subjects was 60.2 (45.0, 63.2) mL/min. One of the 6 subjects had Grade 2 proteinuria. Three subjects were in eGFR category CKD Stage 2, and 3 subjects were in eGFR category CKD Stage 3.

**Efficacy Results:**

***Cohort 1: Switch Subjects***

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm. The virologic success rate was 95.0% (baseline $eGFR_{CG}$ < 50 mL/min 95.0%; baseline $eGFR_{CG}$ ≥ 50 mL/min 95.1%). Three subjects (1.2%) were classified as virologic failures at Week 24. Of those 3 subjects, 2 had HIV-1 RNA ≥ 50 copies/mL at Week 24, and 1 added a new ARV. At Week 24, the virologic success rate by HIV-1 RNA < 20 copies/mL was 93.0% using the FDA snapshot algorithm.

At Week 48, the virologic success rate was 93.7% (164 of 175 subjects; HIV-1 RNA < 50 copies/mL) using the FDA snapshot algorithm. Three subjects (1.7%; all in the baseline $eGFR_{CG}$ ≥ 50 mL/min group) were classified as virologic failures at Week 48. Of those 3 subjects, 1 had HIV-1 RNA ≥ 50 copies/mL at Week 48, 1 discontinued due to lack of efficacy, and 1 added a new ARV.

High rates of virologic suppression were maintained, as assessed using the missing = failure (M = F) (at Week 24) and missing = excluded (M = E) (at Weeks 24 and 48) methods using the Full Analysis Set (FAS). The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 24 were 97.5% and 99.2% for M = F and M =E, respectively. The percentage of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 was 99.4% (M = E).

CD4 cell counts remained stable during treatment with E/C/F/TAF. The mean (SD) baseline CD4 cell count was 664 (286.4) cells/µL. The mean (SD) change from baseline in CD4 cell

counts at Week 24 (observed data) using the FAS was −7 (159.2) cells/μL. The mean (SD) change from baseline in CD4 cell counts through Week 48 (observed data) using the FAS was 16 (158.0) cells/μL.

There were no clinically significant differences in virologic success at Week 24 (FDA snapshot algorithm, HIV-1 RNA < 50 copies/mL) between subgroups (age, sex, race, region, or study drug adherence rate).

***Cohort 2: ART Naive Subjects***

At Week 24, 5 of 6 Cohort 2 ART-naive subjects had HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm. One subject was classified as a virologic failure at Week 24 but had HIV-1 RNA < 50 copies/mL at Week 48.

CD4 cell counts increased during treatment with E/C/F/TAF. Mean (SD) baseline CD4 cell count for the Cohort 2 ART-naive subjects was 412 (244.0) cells/μL. The mean (SD) change from baseline in CD4 cell count through Week 24 (observed data) using the FAS was 126 (106.3) cells/μL. The mean (SD) change from baseline in CD4 cell count through Week 48 (observed data) using the FAS was 144 (169.7) cells/μL.

**Pharmacodynamics Results:**

Statistical comparisons of actual glomerular filtration rate (aGFR) based on iohexol plasma clearance between postbaseline and baseline visits are summarized below using the Pharmacodynamic (PD) Substudy Analysis Set for Cohort 1 switch subjects.

**Table 4. E/C/F/TAF Study GS-US-292-0112: Statistical Analysis and Comparisons of aGFR (mL/min) Between Visits (PD Substudy Analysis Set)**

| Comparison | aGFR (GLSM) | | | | GLSM Ratio (%) | 90% CI |
|---|---|---|---|---|---|---|
| | n | Test Treatment | n | Reference Treatment | | |
| Week 2/4/8 aGFR vs Baseline aGFR (mL/min) | 32 | 59.5 (30.4) | 32 | 60.1 (31.7) | 98.94 | (93.71,104.46) |
| Week 24 aGFR vs Baseline aGFR (mL/min) | 30 | 61.5 (24.9) | 32 | 60.1 (31.7) | 102.66 | (97.11,108.53) |

Actual GFR (aGFR) using iohexol plasma clearance (mL/min) = Iohexol Dose/Iohexol $AUC_{inf}$
It was confirmed that most time points with iohexol concentrations > 2000 μg/mL had blood samples taken from the same arm as iohexol infusion; therefore, time points with iohexol concentrations > 2000 μg/mL were excluded from PK parameter (eg, $AUC_{inf}$) estimates.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 13.3 and 13.4

The geometric least-squares mean (GLSM) ratio and associated 90% CIs for each comparison of aGFR for (1) Week 2, 4, or 8 (ie, the intensive PK visit) versus baseline and (2) Week 24 versus baseline were within the predefined lack of alteration boundary of 80% to 125%. These data indicate that the study treatments did not alter aGFR. Additionally, there were no differences in

aGFR between on-treatment versus baseline when assessed in subgroups according to baseline $eGFR_{CG}$ < 50 mL/min versus $eGFR_{CG}$ ≥ 50 mL/min or in subgroups according to pre-switch TDF use (with or without), as evidenced by the 90% CIs of the GLSM ratios contained within 80% to 125% in all cases.

**Pharmacokinetics Results:**

The plasma PK parameters of E/C/F/TAF in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min are presented in the table below for the PK Substudy Analysis Set:

**Table 5. E/C/F/TAF Study GS-US-292-0112: TAF, TFV, FTC, EVG, and COBI Plasma PK Parameters (PK Analysis Sets)**

| | AUC[a] Mean (%CV) | | $C_{max}$ Mean (%CV) | | $C_{tau}$ Mean (%CV) | |
|---|---|---|---|---|---|---|
| | N | (ng*h/mL) | N | (ng/mL) | N | (ng/mL) |
| TAF[b] | 29 | 254.2 (54.1) | 29 | 265.2 (68.7) | | Not applicable |
| TFV | 29 | 552.7 (32.0) | 30 | 29.3 (29.2) | 25 | 19.2 (31.1) |
| FTC | 29 | 20,968.6 (25.5) | 30 | 2645.3 (24.7) | 26 | 194.2 (33.8) |
| EVG | 28 | 27,107.7 (32.1) | 30 | 2394.3 (31.6) | 26 | 356.9 (75.5) |
| COBI | 29 | 9924.2 (45.2) | 30 | 1290.9 (31.7) | 25 | 38.3 (104.2) |

For each subject in PK substudy, the intensive PK analysis was conducted at Weeks 2, 4, or 8.
All subjects in the PK Substudy Analysis Set are from Cohort 1 (switch).
a $AUC_{tau}$ was calculated for all analytes with the exception of TAF, which was $AUC_{last}$.
b Subject [redacted] (baseline $eGFR_{CG}$ < 50 mL/min) was excluded for sensitivity analysis as TAF PK parameter estimates are unreliable due to an unusual PK profile.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 63.1, 63.2, 63.3, 63.4, and 63.5

TAF PK in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min was consistent with data following administration of E/C/F/TAF in nonrenally impaired HIV-infected subjects in Phase 2 and Phase 3 studies. Specifically, the mean (%CV) TAF $AUC_{last}$ of 254.2 (54.1) ng*h/mL in this study was comparable with TAF $AUC_{last}$ of 227.5 (47.3), 229.8 (33.7), and 259.0 (71.6) ng*h/mL in Phase 2 Study GS-US-292-0102 and Phase 3 Studies GS-US-292-0104 and GS-US-292-0111, respectively. The TAF exposure was numerically higher in subjects with baseline $eGFR_{CG}$ < 50 versus ≥ 50 mL/min, with mean (%CV) TAF $AUC_{last}$ of 340.5 (60.1) ng*h/mL and 226.7 (44.1) ng*h/mL, respectively, and was less than the TAF $AUC_{last}$ of 510.6 (47.4) ng*h/mL in severely renally impaired subjects ($eGFR_{CG}$ 15 to 29 mL/min) in a previous study (Study GS-US-120-0108).

Due to TFV being primarily renally eliminated, TFV PK was higher in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min in this study versus Phase 2 and Phase 3 studies in nonrenally impaired HIV-infected subjects (mean [%CV] TFV $AUC_{tau}$ 552.7 [32.0] ng*h/mL versus 326.2 [14.8], 311.8 [17.1], 286.2 [22.5] ng*h/mL in Phase 2 Study GS-US-292-0102 and Phase 3 Studies GS-US-292-0104 and GS-US-292-0111, respectively). However, TFV exposures were well below the TFV exposure in severely renally impaired subjects ($eGFR_{CG}$ 15-29 mL/min) in Study GS-US-120-0108 (mean $AUC_{inf}$ 2073.8 [47.1] ng*h/mL) and were well below the TFV

exposures from TDF-containing regimens in nonrenally impaired subjects ($eGFR_{CG}$ ≥ 90 mL/min).

Due to FTC being primarily renally eliminated, FTC PK was higher in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min in this study versus the Phase 2 study in nonrenally impaired HIV-infected subjects (mean [%CV] FTC $AUC_{tau}$ 20968.6 [25.5] ng*h/mL versus 11,714.1 [16.6] ng*h/mL in Phase 2 Study GS-US-292-0102). However, the FTC exposure were comparable with the mean FTC exposure achieved in subjects with mild renal impairment not requiring dose adjustment (mean [%CV] FTC AUC 19,900 [6] ng*h/mL). The FTC PK parameters were higher in subjects with baseline $eGFR_{CG}$ < 50 versus ≥ 50 mL/min, consistent with the FTC PK parameters observed in subjects with mild ($eGFR_{CG}$ = 50 to 80 mL/min) or moderate renal impairment ($eGFR_{CG}$ = 30 to 49 mL/min).

Mean (%CV) EVG $AUC_{tau}$ of 27,107.7 (32.1) ng*h/mL and COBI $AUC_{tau}$ of 9924.2 (45.2) ng*h/mL in this study were in the range of data from Phase 2 Study (Study GS-US-292-0102: mean EVG $AUC_{tau}$ 22,797.0 [34.7] ng*h/mL, mean COBI $AUC_{tau}$ 9459.1 [33.9] ng*h/mL). Additionally, EVG and COBI exposure were comparable across eGFR groups in this study (EVG $AUC_{tau}$: 28,705.8 [38.3] and 26,468.4 [29.6] ng*h/mL in subjects with baseline $eGFR_{CG}$ < 50 and ≥ 50 mL/min, respectively; COBI $AUC_{tau}$: 11,316.8 [48.8] and 9393.7 [43.1] ng*h/mL in subjects with baseline $eGFR_{CG}$ < 50 and ≥ 50 mL/min, respectively), consistent with the nonrenal elimination pathway of these agents.

**Safety Results:**

***Cohort 1: Switch Subjects***

In Cohort 1 (switch), the median (Q1, Q3) duration of exposure to study drug was 43.1 (36.1, 48.0) weeks.

Renal Safety

The aGFR was directly measured at baseline, Week 2, 4, and/or 8, and Week 24 using iohexol clearance ($CL_{iohexol}$) for subjects enrolled in the PK/PD substudy (N = 32). Median (Q1, Q3) changes from baseline in aGFR were −1.8 (−5.3, 3.7) mL/min at Week 2, 4, or 8 and 0.1 (−4.3, 4.4) at Week 24. The GLSM ratios (90% CIs) for Week 2, 4, or 8 and Week 24 versus baseline were 98.94 (93.71, 104.46) and 102.66 (97.11, 108.53), respectively, indicating aGFR was not affected by E/C/F/TAF over 24 weeks of treatment.

Median changes from baseline at each time point through Week 48 ranged from −0.01 to 0.04 mg/dL for serum creatinine, −0.06 to −0.01 mg/dL for serum cystatin C, and 0 to 0.3 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters.

The primary renal endpoints were defined as change from baseline at Week 24 in $eGFR_{CG}$, eGFR calculated using the CKD Epidemiology Collaboration (CKD-EPI) cystatin C equation ($eGFR_{CKD\text{-}EPI,\ cysC}$), and eGFR using the CKD-EPI creatinine equation ($eGFR_{CKD\text{-}EPI,\ creatinine}$). No clinically significant changes from baseline eGFR through Week 24 were observed using any of

the 3 equations. The overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at Week 24 was −0.4 (−4.7, 4.5) mL/min for $eGFR_{CG}$, −1.8 (−6.1, 4.9) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.8 (−4.8, 11.2) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ cysC}$. The baseline $eGFR_{CG}$ < 50 mL/min group had median increases from baseline at Weeks 24 and 48 using any of the 3 equations. The baseline $eGFR_{CG} \geq 50$ mL/min group had an increase in eGFR as assessed by $eGFR_{CKD\text{-}EPI,\ cysC}$ and decreases as assessed by $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at Weeks 24 and 48.

Only 2 of 242 subjects (0.8%) (both in the baseline $eGFR_{CG}$ < 50 mL/min group) had an AE in the renal and urinary disorders SOC that led to study drug discontinuation (renal failure and renal failure chronic). Both discontinuations were due to declining glomerular filtration rate: 1 subject had labile hypertension and was using concomitant ramipril and valsartan, and the discontinuation for another subject was assessed as likely related to progression of CKD and not related to study drug. There were no AEs of PRT (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy.

Most subjects had either no change or an improvement (toxicity grade decreased at least 1 grade from baseline) from the baseline proteinuria toxicity grade at Week 24. For 75.0% of subjects (57 of 76) with nonmissing values, the proteinuria grade improved from baseline at Week 24; for only 5.7% of subjects (13 of 230) with nonmissing values, proteinuria grade worsened from baseline at Week 24. For 82.5% of subjects (47 of 57) with pre-switch TDF use who had nonmissing values, the proteinuria grade improved from baseline at Week 24; for only 5.3% of subjects (8 of 151) with nonmissing values, proteinuria grade worsened from baseline at Week 24. For 52.6% of subjects (10 of 19) without pre-switch TDF use and nonmissing values, the proteinuria grade improved from baseline at Week 24; for only 6.3% of subjects (5 of 79) with nonmissing values, proteinuria grade worsened from baseline at Week 24.

More than half of subjects (57.0%, 53 of 93 subjects with nonmissing values) with clinically significant proteinuria (UPCR > 200 mg/g) at baseline had no clinically significant proteinuria by Week 24. Only 8 of 133 subjects (6.0%) developed clinically significant proteinuria (UPCR > 200 mg/g) by Week 24. Nearly half of subjects (47.2%, 50 of 106) with clinically significant albuminuria (UACR ≥ 30 mg/g) at baseline had no clinically significant albuminuria (< 30 mg/g) by Week 24. Only 4 of 117 subjects (3.4%) developed clinically significant albuminuria (UACR ≥ 30 mg/g) by Week 24.

Clinically significant proteinuria was defined as UPCR > 200 mg/g, and clinically significant albuminuria was defined as UACR ≥ 30 mg/g. Decreases in UPCR from the baseline median of 160.6 mg/g were observed at Week 1 (median of 110.3 mg/g) and persisted through Week 48 (median of 80.1 mg/g). Median UPCR percentage changes from baseline for Weeks 1 to 48 ranged from −27.3% to −47.1%. For subjects with baseline $eGFR_{CG}$ < 50 mL/min, median baseline UPCR was 270.0 mg/g, and medians for Weeks 1 to 48 ranged from 130.0 to 209.0 mg/g with median percentage changes from baseline ranging from −23.8% to −40.1%; for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median baseline UPCR was 138.5 mg/g, and medians for Weeks 1 to 48 ranged from 68.9 to 88.9 mg/g with median percentage changes from baseline ranging from −28.7% to −47.7%. Similar to UPCR, decreases in UACR from the baseline median of 28.8 mg/g were observed at Week 1 (median of 16.6 mg/g) and persisted through Week 48 (median of 8.3 mg/g). Median UACR percentage changes from baseline for

Weeks 1 to 48 ranged from −33.7% to −52.3%. For subjects with baseline $eGFR_{CG}$ < 50 mL/min, median baseline UACR was 53.2 mg/g, and medians for Weeks 1 to 48 ranged from 25.2 to 34.9 mg/g with median percentage changes from baseline ranging from −28.2% to −42.6% for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median baseline UACR was 22.7 mg/g, and medians for Weeks 1 to 48 ranged from 6.5 to 11.3 mg/g with median percentage changes from baseline ranging from −33.8% to −53.2%.

Decreases in median percentage change from baseline in urine RBP to creatinine ratio (baseline of 800.5 µg/g) and beta-2-microglobulin to creatinine ratio (baseline of 1562.5 µg/g) were observed from Weeks 1 to 48: RBP to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −71.9% to −43.4%; beta-2-microglobulin to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −80.5% to −48.2%.

No clinically significant changes from baseline through Week 48 were observed for renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR), fractional excretion of phosphate ($FEPO_4$), FEUA, or urine creatinine overall or for the baseline $eGFR_{CG}$ < 50 mL/min and $eGFR_{CG} \geq 50$ mL/min groups.

Adverse Events

At least 1 AE was reported in 86.4% of Cohort 1 switch subjects (n = 209: 67 [83.8%] with baseline $eGFR_{CG}$ < 50 mL/min and 142 [87.7%] with baseline $eGFR_{CG} \geq 50$ mL/min). No subjects died during this study.

A total of 10.7% of subjects reported at least 1 SAE (n = 26: 9 [11.3%] with baseline $eGFR_{CG}$ < 50 mL/min and 17 [10.5%] with baseline $eGFR_{CG} \geq 50$ mL/min); all SAEs were considered unrelated to study drug by the investigator. The AEs considered related to study drug by the investigator were reported in 25.6% of subjects (n = 62: 21 [26.3%] with baseline $eGFR_{CG}$ < 50 mL/min and 41 [25.3%] with baseline $eGFR_{CG} \geq 50$ mL/min). At least 1 Grade 3 or 4 AE was reported in 7.4% of subjects (n = 18: 7 [8.8%] with baseline $eGFR_{CG}$ < 50 mL/min and 11 [6.8%] with baseline $eGFR_{CG} \geq 50$ mL/min); of these, 3 subjects had Grade 3 or 4 AEs considered related to study drug by the investigator: blood creatine phosphokinase increased (baseline $eGFR_{CG}$ < 50 mL/min group), gastroesophageal reflux disease (baseline $eGFR_{CG}$ ≥ 50 mL/min group), and hypercholesterolemia (baseline $eGFR_{CG} \geq 50$ mL/min group).

The AEs leading to premature study drug discontinuation were reported in 3.3% of subjects (n = 8; 6 [7.5%] with baseline $eGFR_{CG}$ < 50 mL/min and 2 [1.2%] with baseline $eGFR_{CG}$ ≥ 50 mL/min); of these, 3 subjects (2 with baseline $eGFR_{CG}$ < 50 mL/min and 1 with baseline $eGFR_{CG} \geq 50$ mL/min) had a single AE leading to premature study drug discontinuation considered related to study drug by the investigator (worsening of sleep disturbance, worsening renal insufficiency, and choking, respectively).

The most commonly reported AEs were diarrhea (8.7%, 21 subjects), arthralgia (8.3%, 20 subjects), and bronchitis and osteopenia (7.9%, 19 subjects for each AE). Of note, 16 of 19 subjects had the AE of osteopenia reported on Day 1, suggesting that these AEs were most likely reported based on the baseline (predose) dual-energy x-ray absorptiometry (DXA) scan and were not truly treatment emergent; the other 3 subjects had the AE of osteopenia reported

within 12 days after the first dose of study drug. The most commonly reported AEs considered related to the study drug by the investigator were dizziness (2.9%, 7 subjects), diarrhea (2.5%, 6 subjects), and headache (2.1%, 5 subjects). Importantly, rates of AEs associated with FTC were low despite higher FTC exposure in the $eGFR_{CG} < 50$ mL/min group.

Bone Safety

A total of 5 subjects (2.1%) experienced 6 fracture events, of whom 4 were subjects with pre-switch TDF use and 1 was a subject without pre-switch TDF use. All reported fracture AEs were considered unrelated to study drug by the investigator, and none resulted in discontinuation of study drug. All fracture events were the result of trauma, and none were reported as fragility fractures.

Overall, hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF: mean (SD) percentage increases from baseline were observed in hip BMD (Week 24: 0.733% [2.7674]; Week 48: 1.575% [4.5738]) and spine BMD (Week 24: 1.643% [3.6250]; Week 48: 2.368% [4.2582]). Mean percentage changes from baseline in hip and spine BMD for those with pre-switch TDF use compared with those without pre-switch TDF use were 1.151% versus −0.071% for hip BMD and 2.370% versus 0.291% for spine BMD at Week 24 and 1.843% versus 0.997% for hip BMD and 2.994% versus 1.104% for spine BMD at Week 48. There was evidence for an improvement in hip and spine BMD after switch to E/C/F/TAF when assessed using a threshold of 3% for changes from baseline; higher percentages of subjects had increases versus decreases from baseline in BMD at both hip (Week 24: 13.8% versus 7.1%; Week 48: 22.4% versus 6.2%) and spine (Week 24: 33.6% versus 8.0%; Week 48: 38.8% versus 4.4%). In addition, few changes from baseline at Weeks 24 and 48 were observed in hip and spine BMD clinical status.

Median percentage changes from baseline at Weeks 24 and 48 were observed in the bone turnover biomarkers C-telopeptide and procollagen type 1 N-terminal propeptide (P1NP), as well as parathyroid hormone (PTH). For each of the bone biomarkers and PTH, subjects with pre-switch TDF use had median percentage decreases from baseline at Weeks 24 and 48, whereas those without pre-switch TDF use had median percentage increases from baseline at Weeks 24 and 48. Median (Q1, Q3; baseline value) percentage changes from baseline at Week 24 for subjects with and without pre-switch TDF use were as follows: C-telopeptide: with pre-switch TDF use −5.4% (−19.2%, 7.1%; 4.8 µg/L), without pre-switch TDF use 5.2% (−8.1%, 21.3%; 5.1 µg/L); PINP: with pre-switch TDF use −24.27% (−39.98%, −8.34%; 57.21 ng/mL), without pre-switch TDF use 8.94% (−15.64%, 43.64%; 45.43 ng/mL); PTH: with pre-switch TDF use −15.9% (−32.0%, 8.1%; 48.3 pg/mL), without pre-switch TDF use 14.6% (−9.3%, 65.2%; 43.4 pg/mL).

Ocular Safety

Adverse events in the eye disorders SOC were reported in 22 of 242 subjects (9.1%), 6 of 80 subjects (7.5%) with baseline $eGFR_{CG} < 50$ mL/min and 16 of 162 subjects (9.9%) with baseline $eGFR_{CG} \geq 50$ mL/min. None of the AEs in the eye disorders SOC were serious, resulted in discontinuation of study drug, or were considered representative of an actual case of clinical uveitis.

Laboratory Abnormalities

There were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters through Week 48. The majority of reported laboratory abnormalities were Grade 1 or Grade 2. The most commonly observed Grade 3 or 4 laboratory abnormalities in Cohort 1 switch subjects were LDL (fasting) (Grade 3, 14 subjects), creatine kinase (Grade 3, 8 subjects; Grade 4, 2 subjects), serum glucose (nonfasting, hyperglycemia) (Grade 3, 8 subjects; Grade 4, 2 subjects), and total cholesterol (fasting, hypercholesterolemia (Grade 3, 10 subjects). Importantly, rates of laboratory abnormalities associated with FTC were low despite higher FTC exposure in the $eGFR_{CG} < 50$ mL/min group.

Metabolic Laboratory Parameters

For subjects from each baseline $eGFR_{CG}$ group in Cohort 1, median changes from baseline to Weeks 24 or 48 were observed while fasting for total cholesterol, direct LDL cholesterol, HDL cholesterol, total cholesterol to HDL ratio, triglycerides, and glucose demonstrated a trend toward increase in most parameters evaluated. Median changes from baseline in metabolic laboratory parameters at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects with pre-switch TDF use and a decrease in most parameters for subjects without pre switch TDF use.

***Cohort 2: ART Naive Subjects***

In Cohort 2 (ART naive), the median (Q1, Q3) duration of exposure to study drug was 42.8 (36.1, 48.1) weeks. The majority of the subjects (83.3%, 5 subjects) received study drug for ≥ 36 weeks. Only 6 Cohort 2 ART-naive subjects were enrolled; therefore, limited summaries are provided for these subjects, and interpretation of their data should be made with caution.

Renal Safety

Median changes from baseline in serum creatinine at each time point through Week 48 ranged from −0.01 to 0.13 mg/dL, indicating no clinically significant changes in serum creatinine in these subjects. Graded serum creatinine laboratory abnormalities (Grade 1 only) were reported for 1 subject. Median changes from baseline at each time point through Week 48 ranged from −0.13 to 0.19 mg/dL for serum cystatin C and −0.6 to 0.2 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters.

The median (Q1, Q3) change from baseline in eGFR at Week 24 (primary endpoint) was −0.3 (−3.6, 1.3) mL/min for $eGFR_{CG}$, −2.6 (−11.1, −0.9) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.9 (−3.3, 13.2) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ cysC}$.

No renal SAEs or AEs in the renal and urinary disorders SOC that led to study drug discontinuation were reported. There were no AEs of PRT (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy.

No changes from the baseline proteinuria toxicity grade were observed. Changes from baseline in median UPCR and UACR were observed, but no subject developed new clinically significant

proteinuria (UPCR > 200 mg/g) or clinically significant albuminuria (UACR > 30 mg/g). Changes in UPCR from the baseline median of 45.9 mg/g were observed from Weeks 1 to 48, with medians of 50.8, 48.8, 48.7, 48.4, 55.0, 43.2, 58.2, 48.9, and 59.9 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively. Changes in UACR from the baseline median of 12.3 mg/g were observed from Weeks 1 to 48, with medians of 5.3, 7.8, 10.4, 8.1, 8.9, 7.2, 12.4, 7.1, and 8.6 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively.

Changes in urine RBP to creatinine ratio were observed from Weeks 1 to 48, with median percentage changes from baseline of 12.1%, −20.8%, −5.0%, −9.6%, 68.8%, and 69.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively. Changes in beta-2-microglobulin to creatinine ratio were observed from Weeks 1 to 48, with median percentage changes from baseline of −15.2%, 43.4%, −47.1%, −10.2%, −19.5%, and 34.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively.

No clinically significant changes from baseline through Week 48 were observed for TmP/GFR, $FEPO_4$, or FEUA.

Adverse Events

At least 1 AE was reported for 5 Cohort 2 ART-naive subjects, any Grade 2, 3, or 4 AE was reported in 3 subjects, and a Grade 2 AE considered related to study drug by the investigator was reported in 1 subject. No SAEs, Grade 3 or 4 AEs, or AEs leading to study drug discontinuation were reported for this cohort, and no individual AE occurred in > 1 subject. No subjects died during this study.

Bone Safety

No fracture events occurred in Cohort 2 ART-naive subjects. Mean (SD) percentage changes from baseline were observed in hip BMD (Week 24: 0.022% [1.6853]; Week 48: −0.222% [2.3207]) and spine BMD (Week 24: −2.686 [4.5755]; Week 48: −4.538 [6.8917]) for subjects after switching to E/C/F/TAF. Change from baseline for hip and spine BMD was < 3% in Cohort 2 (ART naive). Overall, few subjects had changes from baseline in hip and spine BMD clinical status.

Ocular Safety

No Cohort 2 ART-naive subjects had an AE reported in the SOC of eye disorders.

Laboratory Abnormalities

There were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters through Week 48. The majority of reported laboratory abnormalities were Grade 1 or Grade 2. One Grade 3 (amylase) and 1 Grade 4 (creatine kinase) laboratory abnormality was observed in a single Cohort 2 ART naive subject, neither of which was reported as an AE.

Metabolic Laboratory Parameters

Among the 6 ART-naive subjects in Cohort 2, no Grade 3 to 4 fasting total cholesterol, triglycerides, or LDL abnormalities were reported. Four subjects had Grade 1 and 2 subjects had Grade 2 hypercholesterolemia. No subjects had graded triglyceride values. Two subjects had Grade 1 and 3 subjects had Grade 2 increased fasting LDL. One subject had Grade 2 fasting hyperglycemia and 1 subject had Grade 1 fasting hypoglycemia). One subject had an AE of hyperlipidemia considered related to study drug by the investigator.

**Other Outcome Measures:**

Most subjects did not require hospitalization, unplanned visits for a healthcare issue, or unplanned specialty care provider visits. No clinically meaningful trends or changes at any assessment time point were observed.

**CONCLUSIONS:**

The interim Week 24 conclusions from this study are as follows:

- Cohort 1 subjects who switched treatment to E/C/F/TAF maintained virologic suppression and had increases in CD4 counts.
- The PK of the individual components of E/C/F/TAF in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min was consistent with historical and concurrent data on these agents.
- While TFV PK was higher in subjects with mild and moderate renal impairment, TFV exposures were well below those in patients with severe renal impairment and were well below the TFV exposures from TDF-containing regimens.
- Despite higher FTC PK in this study, once daily administration of E/C/F/TAF without dose adjustment in subjects with baseline $eGFR_{CG} < 50$ mL/min did not have a different safety profile compared with subjects with baseline $eGFR_{CG} < 50$ mL/min and despite Emtriva® dose recommendations, E/C/F/TAF does not require dose adjustment in patients with $eGFR_{CG} \geq 30$ to $< 50$ mL/min.
- Cohort 1 switch subjects had no change in aGFR through 24 weeks, regardless of baseline $eGFR_{CG}$ or pre-switch TDF use.
- E/C/F/TAF was generally well tolerated, with no on-study deaths and low rates of SAEs, discontinuations of study drug due to AEs, and AEs considered related to study drug by the investigator.
- No notable changes from baseline in median values for hematology, clinical chemistry, or liver related laboratory parameters were observed in either cohort through Week 48, and the majority of reported laboratory abnormalities were Grade 1 or 2.

- Median changes from baseline in metabolic laboratory parameters at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects who received TDF at baseline and a trend toward decrease in most parameters for subjects who did not receive TDF at baseline.
- The rate of study drug discontinuation due to renal AEs was low, and no AEs of proximal renal tubulopathy (PRT; including Fanconi Syndrome) were reported.
- No clinically significant effects of E/C/F/TAF on serum creatinine or cystatin C estimates of glomerular function in Cohort 1 switch and Cohort 2 ART-naive subjects were observed.
- Multiple assessments of renal function indicate that significant improvements in renal function occur as soon as 1 week after switch to E/C/F/TAF and persist through 24 and/or 48 weeks, including significant improvements in proteinuria, albuminuria, tubular proteinuria, and fractional excretion of uric acid (FEUA). No notable trends in changes from baseline through Week 48 were observed for TmP/GFR, fractional excretion of phosphate ($FEPO_4$), urine FEUA, or urine creatinine.
- There were decreases in clinically significant proteinuria (UPCR > 200 mg/g) or albuminuria (UACR ≥ 30 mg/g) through Week 48 in a notable proportion of subjects.
- These improvements in renal function observed after switch to E/C/F/TAF may be of substantial clinical significance for HIV-infected patients taking lifelong ARV therapy and accumulating age-related comorbidities.
- Switch to E/C/F/TAF generally resulted in improvements in BMD over 24 and/or 48 weeks. No fragility fractures were reported.
- E/C/F/TAF may be administered once daily without dose adjustment in patients with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min), and after switching to E/C/F/TAF, rapid, clinically significant improvements in renal and bone safety occur.

#### 1.1.4.1.2. ART-Naive Adolescent Subjects in Study GS-US-292-0106

A complete study description and results for Study GS-US-292-0106 are available in the CSR (GS-US-292-0106 Interim CSR), and a brief narrative of this study is presented below.

**Title of Study:** A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents

**Objectives:** Study GS-US-292-0106 is being conducted to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF in HIV-infected, ART-naive adolescents.

The primary objectives of this ongoing study are as follows:

Part A:

- To evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC in HIV-infected, ART-naive adolescents

Part B:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 24 in HIV-infected, ART-naive adolescents

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 48 in HIV-infected, ART-naive adolescents

- To evaluate the antiviral activity of the E/C/F/TAF FDC through Week 48 in HIV-infected, ART-naive adolescents

The current report (interim Week 24 analysis) describes the results of the study through the date when all subjects enrolled by 11 February 2014 had completed their Week 24 visit.

Acceptability and palatability assessments are also being conducted as a part of the study; those results will be presented in a future CSR.

**Diagnosis and Main Criteria for Inclusion:** Subjects enrolled in this study were HIV-infected, ART-naive adolescents, 12 to < 18 years of age, weight ≥ 35 kg, with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell counts > 100 cells/μL, and eGFR ≥ 90 mL/min/1.73 $m^2$ (as calculated using the Schwartz formula) at screening, with no prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother to child transmission) and sensitivity to TFV, EVG, and FTC as demonstrated by HIV-1 genotyping at screening.

**SUMMARY OF RESULTS:**

**Subject Disposition and Demographics:** Of 63 screened subjects, 48 were enrolled into the study (24 in Part A and 24 in Part B) and received at least 1 dose of E/C/F/TAF.

At the time of the interim Week 24 analysis, 2.1% (1 subject) had completed the main phase of the study (ie, 48 weeks), and 97.9% (47 subjects) were still on study. The subject who completed the main phase of the study entered into the extension phase and was receiving study drug.

In the Safety Analysis Set, 58.3% of subjects were female. The median age of subjects was 15 years (range: 12 to 17); all of the subjects were either black (87.5%), or Asian (12.5%), and none were Hispanic or Latino.

The median (Q1, Q3) body weight of subjects at baseline was 52.0 (40.5, 60.5) kg; and the median (Q1, Q3) baseline Z-score for weight was −0.37 (−1.12, 0.47). The median (Q1, Q3)

baseline height was 157.3 (147.2, 166.7) cm; and the median (Q1, Q3) baseline Z-score for height was −0.81 (−1.81, 0.05). The median (Q1, Q3) value for BMI at baseline was 20.0 (18.1, 23.2) kg/m$^2$, and the median (Q1, Q3) baseline eGFR calculated using the Schwartz and modified Schwartz formulas was 157.5 (133.0, 187.0) mL/min/1.73 m$^2$ and 110.9 (95.8, 118.8) mL/min/1.73 m$^2$, respectively. For males, the most frequently observed stage for pubic hair and genitalia was Tanner Stage 5 (45.0% each). For females, the most frequently observed stages for pubic hair were Tanner Stages 3 and 5 (25.0% each); and the most frequently observed Tanner stage for breasts was Stage 5 (32.1%).

The median (Q1, Q3) baseline HIV-1 RNA value was 4.65 (4.24, 4.94) $\log_{10}$ copies/mL. Overall, 20.8% of subjects had baseline HIV-1 RNA > 100,000 copies/mL. Median (Q1, Q3) baseline CD4 cell count was 452 (326, 563) cells/μL; 64.6% of subjects had CD4 cell counts < 500 copies/mL, and 27.1% had CD4 cell counts < 350 copies/mL. The median (Q1, Q3) CD4% was 23.0% (17.3, 30.3). The most common risk factor for HIV infection was vertical transmission (66.7%), followed by heterosexual sex (20.8%), and homosexual sex (12.5%). The majority of subjects (83.3%) had asymptomatic HIV-1 infection. None of the subjects were hepatitis B virus (HBV) surface antigen positive. One subject (2.1%) was hepatitis C virus (HCV) antibody positive at baseline, but had a negative confirmatory HCV polymerase chain reaction result.

**Efficacy Results:** At the interim Week 24 analysis, the virologic success rate was 91.3% (21 of 23 subjects in the Week 24 FAS) for HIV-infected, ART-naive adolescents receiving E/C/F/TAF (assessed using the FDA snapshot algorithm with a cutoff of HIV-1 RNA < 50 copies/mL). Two subjects who had HIV-1 RNA > 50 copies/mL at Week 24 had HIV-1 RNA < 50 copies/mL at earlier visits and at Week 32.

HIV-1 RNA outcomes were similar for the M = F (Week 24 FAS) and M = E (FAS) analyses. At Week 24, 91.3% had HIV-1 RNA < 50 copies/mL, and 95.7% had HIV-1 RNA < 400 copies/mL.

HIV-1 RNA levels decreased following initiation of E/C/F/TAF (FAS), with a mean (SD) decrease of 3.16 (0.511) $\log_{10}$ copies/mL by Week 8. At Week 24, the mean (SD) change from baseline in HIV-1 RNA was −3.34 (0.679) $\log_{10}$ copies/mL.

No subject met the protocol-specified criteria for postbaseline resistance analysis (suboptimal virologic response or virologic rebound); thus, there was no evidence of virologic resistance to E/C/F/TAF in any subject.

CD4 cell count and percentage increased following initiation of study drug, and continued to increase with increased duration of exposure to study drug (FAS). Mean (SD) baseline CD4 cell count was 468 (215.4) cells/μL, and at Week 24, the mean (SD) change from baseline in CD4 cell count was 212 (144.3) cells/μL. Mean (SD) baseline CD4% was 23.5% (8.93%), and at Week 24, the mean (SD) change from baseline in CD4% was 7.2% (4.97%).

**Pharmacokinetics Results:** The PK parameters for EVG, TAF, TFV, COBI, and FTC were analyzed for the 24 subjects enrolled in Part A; statistical comparisons were performed of PK data from adolescents who received E/C/F/TAF in Part A of this study and combined PK data from the adult comparator.

**Table 6. E/C/F/TAF Study GS-US-292-0106: Statistical Comparisons of EVG, TAF, TFV, COBI, and FTC PK Parameter Estimates Between Adolescents and Adults (PK Analysis Sets)**

| PK Parameter | GLSMs | | GLSM Ratio (%) | 90% CI |
|---|---|---|---|---|
| | GS-US-292-0106 (Test) (N = 24) | GS-US-292-0102, GS-US-292-0103 (Reference) (N = 52) | | |
| **EVG** | | | | |
| $AUC_{tau}$ (ng*h/mL) | 23128.88 | 21865.51 | 105.78 | 94.66, 118.21 |
| $C_{max}$ (ng/mL) | 2186.24 | 2023.29 | 108.05 | 97.87, 119.30 |
| $C_{trough}$ (ng/mL) | 234.44 | 338.24 | 69.31 | 52.79, 91.01 |
| **TAF** | | | | |
| $AUC_{last}$ (ng*h/mL) | 159.50 | 225.53 | 70.72 | 56.12, 89.11 |
| $C_{max}$ (ng/mL) | 135.19 | 173.97 | 77.71 | 59.88, 100.85 |
| **TFV** | | | | |
| $AUC_{tau}$ (ng*h/mL)[a] | 282.64 | 322.64 | 87.60 | 81.23, 94.47 |
| $C_{max}$ (ng/mL) | 17.18 | 18.78 | 91.50 | 83.93, 99.75 |
| $C_{trough}$ (ng/mL) | 9.73 | 11.20 | 86.94 | 79.73, 94.81 |
| **COBI** | | | | |
| $AUC_{tau}$ (ng*h/mL)[a] | 7762.56 | 9832.00 | 78.95 | 68.68, 90.75 |
| $C_{max}$ (ng/mL) | 1144.60 | 1456.27 | 78.60 | 69.71, 88.62 |
| $C_{trough}$ (ng/mL)[b,c] | 13.42 | 22.21 | 60.41 | 39.13, 93.26 |
| **FTC** | | | | |
| $AUC_{tau}$ (ng*h/mL) | 14,007.48 | 11,964.30 | 117.08 | 106.68, 128.49 |
| $C_{max}$ (ng/mL) | 2209.14 | 1947.42 | 113.44 | 103.49, 124.35 |
| $C_{trough}$ (ng/mL)[a] | 94.98 | 97.42 | 97.49 | 83.42, 113.94 |

a N = 23 for the Test group
b N = 15 for the Test group
c N = 51 for the Reference group
Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 51.1, 51.2, 51.3, 51.4 and 51.5

The 90% CIs of the GLSM ratios for EVG $AUC_{tau}$ and $C_{max}$ were contained within the predefined equivalence boundaries of 70% to 143%, indicating that exposure of EVG in adolescents receiving E/C/F/TAF was comparable with that in adult subjects. Additionally, EVG $C_{trough}$ was above the protein binding-adjusted concentration that resulted in 95% inhibition ($IC_{95}$) (44.5 ng/mL) in all adolescent subjects. TAF $AUC_{last}$ and $C_{max}$ following E/C/F/TAF administration to adolescents in this study were 29.28% and 22.29% lower, respectively, than exposure in the adult comparator, which was based on available adult PK data. These differences were not considered clinically relevant, as the TAF exposure observed in adolescents was consistent with the range of exposure associated with antiviral activity in adults. Moreover, the 90% CI of the GLSM ratios for TFV $AUC_{tau}$, $C_{max}$, and $C_{trough}$ were contained within the predefined equivalence boundaries of 70% to 143%. TFV exposure in adolescents following E/C/F/TAF administration was approximately 90% lower compared with TFV exposure in adults following STB administration and coadministration of TDF with boosted PIs. The 90% CIs of

the GLSM ratios for FTC $AUC_{tau}$, $C_{max}$, and $C_{trough}$ were contained within the predefined equivalence boundaries of 70% to 143%. COBI $AUC_{tau}$, $C_{max}$, and $C_{trough}$ in adolescents were 21.05%, 21.40%, and 39.59% lower, respectively, compared with the adult comparator; however, they were in the range of exposure observed in historical studies that was associated with a robust pharmacodynamic effect (boosting), which is the function of COBI in E/C/F/TAF.

**Safety Results:** E/C/F/TAF was well tolerated by the 48 HIV-infected, ART-naive adolescents in this study, through a median duration of exposure of 12.1 weeks. Overall, 47.9% (23 subjects) had received study drug for ≥ 24 weeks. One or more AEs were reported for most subjects (81.3%; 39 of 48 subjects), most of which were Grade 1 or 2 in severity. The most common AEs were nausea (22.9%, 11 subjects), upper respiratory tract infection (20.8%, 10 subjects), and diarrhea (16.7%, 8 subjects). Eighteen subjects (37.5%) had an AE considered related to study drug by the investigator, most of which were Grade 1 in severity. Four subjects (8.3%) had a Grade 3 or 4 AE. Study drug-related AEs that occurred in > 1 subject were either gastrointestinal, including nausea (20.8%, 10 subjects), abdominal pain (12.5%, 6 subjects), vomiting (10.4%, 5 subjects), upper abdominal pain (6.3%, 3 subjects), and diarrhea (6.3%, 3 subjects), or nervous system disorders, including somnolence (6.3%, 3 subjects), dizziness (4.2%, 2 subjects), and headache (4.2%, 2 subjects). Four subjects (8.3%) had a SAE. One subject had Grade 2 visual impairment and uveitis reported as SAEs considered related to study drug by the investigator that resolved while study drug continued. No subject had an AE that led to study drug discontinuation, and there were no deaths.

Prespecified AEs of interest were selected renal events and bone fractures. One subject had urinary retention of 6 days' duration reported as an SAE considered unrelated to study drug by the investigator; study drug dosing was not interrupted. No subject had a bone fracture.

The median (Q1, Q3) change from baseline in serum creatinine was 0.06 (0.00, 0.13) mg/dL at Week 1 (baseline median [Q1, Q3], 0.57 [0.50, 0.71] mg/dL). Creatinine subsequently stabilized without progressive changes; median (Q1, Q3) change from baseline at Week 24 was 0.08 (0.04, 0.17) mg/dL. No graded abnormalities of serum creatinine were reported.

The median (Q1, Q3) change from baseline in eGFR (calculated using the Schwartz formula) at Week 1 was −14.0 (−27.0, −1.0) mL/min/1.73 $m^2$ (baseline median [Q1, Q3], 157.5 [133.0, 187.0] mL/min/1.73 $m^2$). The median (Q1, Q3) change from baseline at Week 24 was −20.0 (−32.0, −12.0) mL/min/1.73 $m^2$.

No AEs of decreased eGFR or renal failure were reported.

The median (Q1, Q3) change from baseline in cystatin C at Week 24 was −0.10 (−0.16, −0.04) mg/L (baseline median [Q1, Q3], 0.74 [0.68, 0.82] mg/L.

At baseline, 4.2% (2 of 48 subjects) had Grade 1 or Grade 2 proteinuria as assessed by dipstick analysis. Postbaseline, treatment-emergent Grade 1 or Grade 2 proteinuria, generally isolated and transient, was reported for 20.8% (10 of 48 subjects). Proteinuria was not reported as an AE for any subject.

There were no clinically meaningful changes from baseline in proteinuria, as assessed by UPCR (median [Q1, Q3]: baseline, 86.14 [41.49, 139.29] mg/g; percentage change from baseline at Week 24, 9.29% [−27.59%, 47.83%]). A reduction from baseline was observed at Week 24 in the urine beta-2-microglobulin to creatinine ratio, an exploratory marker of renal tubular proteinuria (median [Q1, Q3]: baseline, 179.16 [92.31, 264.71] µg/g; percentage change from baseline at Week 24, −44.61% [−72.46%, −21.00%]). No clinically meaningful change from baseline in urine RBP to creatinine ratio, TmP/GFR, $FEPO_4$, or FEUA was observed through Week 24.

No subject had laboratory findings consistent with PRT.

Mean and median baseline values and percentage changes from baseline at Week 24 in spine and TBLH BMD are shown in the following table.

**Table 7. E/C/F/TAF Study GS-US-292-0106: Baseline Value and Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD at Week 24 (Spine and TBLH DXA Analysis Sets)**

| | Spine (N = 23) | | TBLH (N = 23) | |
|---|---|---|---|---|
| **Time Point** | **Mean (SD)** | **Median (Q1, Q3)** | **Mean (SD)** | **Median (Q1, Q3)** |
| Baseline ($g/cm^2$) | 0.779 (0.2102) | 0.778 (0.677, 0.838) | 0.872 (0.1305) | 0.856 (0.805, 0.935) |
| % Change at Week 24 | 1.726 (4.2840) | 2.773 (−1.182, 4.557) | 0.772 (2.5631) | 0.340 (−1.228, 2.122) |

Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 36.1 and 36.2

At Week 24, 2 of 23 subjects (8.7%) had a ≥ 4% decrease in spine BMD; no subject had a ≥ 4% decrease in TBLH BMD.

Baseline height-age adjusted spine and TBLH BMD Z-scores were higher than unadjusted Z-scores (consistent with the below average height of the study population). Baseline and changes from baseline in spine and TBLH height-age adjusted BMD Z-scores at Week 24 are shown in the following table.

**Table 8. E/C/F/TAF Study GS-US-292-0106: Spine and Total-Body-Less-Head Height-Age Adjusted BMD Z-Scores at Baseline and Change from Baseline at Week 24 (Spine and TBLH DXA Analysis Sets)**

| | Spine BMD Z-Score (Height-Age Adjusted) (N = 21) | | TBLH BMD Z-Score (Height-Age Adjusted) (N = 20) | |
|---|---|---|---|---|
| | **Mean (SD)** | **Median (Q1, Q3)** | **Mean (SD)** | **Median (Q1, Q3)** |
| **Baseline** | –0.84 (1.201) | –0.75 (–1.86, 0.09) | –0.44 (1.007) | –0.66 (–1.24, 0.48) |
| **Change from Baseline at:** | | | | |
| **Week 24** | –0.08 (0.391) | –0.02 (–0.15, 0.13) | –0.10 (0.256) | –0.09 (–0.26, 0.10) |

Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 37.3 and 37.4

An increase in serum PTH was observed; the median (Q1, Q3) values at baseline and Week 24 were 35.8 (28.6, 53.7) and 44.3 (35.7, 52.0) pg/mL, respectively; the median (Q1, Q3) percentage change from baseline at Week 24 was 33.4% (12.6%, 60.6%).

There were no clinically relevant changes from baseline in median values for any hematology or clinical chemistry parameter. Increases from baseline in the following fasting lipid parameters were observed at Week 24 (median [Q1, Q3] change from baseline: fasting total cholesterol, 34 [22, 41] mg/dL; fasting LDL cholesterol, 18 [5, 30] mg/dL; and fasting HDL cholesterol, 10 [4, 21] mg/dL).

Most subjects had at least 1 treatment-emergent laboratory abnormality reported during the study (81.3%, 39 of 48 subjects). The majority of abnormalities reported were Grade 1 or 2 in severity. Excluding Grade 3 hematuria detected by nonquantitative dipstick analysis, Grade 3 laboratory abnormalities were reported for 4 subjects. Grade 3 decreased neutrophils were reported for 3 subjects. One subject had transient Grade 3 hematuria following quantitative analysis. None of these laboratory abnormalities was reported as an AE.

**CONCLUSIONS:**

The interim Week 24 conclusions from this study are as follows:

- Based on PK analyses, the dose of E/C/F/TAF (150/150/200/10 mg) is appropriate for adolescent use. Specifically:
  - EVG exposure in adolescents administered E/C/F/TAF was similar to that in adults.
  - TAF exposure in adolescents was consistent with the range of exposure associated with antiviral activity in adults, despite being lower than that in the adult comparator.
  - TFV exposure in adolescents was similar to that in adults.
  - FTC exposure in adolescents was consistent with adult data.
  - COBI exposure in adolescents was lower compared with the adult comparator, but was consistent with the totality of historical data and in the range of exposure associated with robust pharmacoenhancement (boosting).
- Nearly all ART-naive adolescents who received E/C/F/TAF achieved virologic suppression to < 50 copies/mL at Week 24 (91.3% virologic success rate), further confirming the E/C/F/TAF 150/150/200/10 mg dose in adolescents.
- There was evidence of a robust immunological response to E/C/F/TAF in treatment-naive adolescents. Mean (SD) CD4 cell count and CD4% were 639 (254.0) cells/μL and 29.6% (9.54%), respectively, at Week 24, representing mean (SD) increases from baseline of 212 (144.3) cells/μL and 7.2% (4.97%), respectively.

- E/C/F/TAF was well tolerated, as evidenced by the low incidence of SAEs and the absence of AEs leading to discontinuation of study drug.

- The lack of notable changes from baseline in height-age adjusted spine and TBLH BMD Z-scores at Week 24 indicates that subjects mineralized bone at rates consistent with those of the reference population. Few subjects experienced a clinically relevant decrease from baseline in BMD at Week 24.

- Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration.

#### 1.1.4.2. RPV Studies

Narrative safety data are provided in this section for ART-naive adolescent subjects receiving RPV (C213; Section 1.1.4.2.1).

##### 1.1.4.2.1. ART-Naive Adolescent Subjects in Study C213

A complete study description and results for Study C213 are available in the CSR (TMC278-C213-W48-CSR), and a brief narrative of this study is presented below.

**Title of Study:** A Phase II, open-label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of TMC278 in antiretroviral-naive HIV-1 infected adolescents aged 12 to <18 years

**Objectives:** The objectives of Part 1 of this study were:

- to evaluate the steady-state pharmacokinetics of rilpivirine (RPV; previously known as TMC278) 25 mg quaque die (qd; once daily) in subjects aged ≥12 to <18 years;

- to evaluate short-term safety and antiviral activity of RPV in this age group.

The objectives of Part 2 of this study were:

- to evaluate long-term safety and efficacy over a 24- and 48-week treatment period of RPV;

- to evaluate immunologic changes (as measured by CD4+ cell parameters) over a 24- and 48-week treatment period of RPV;

- to assess the evolution of viral genotype and phenotype over a 24- and 48-week treatment period of RPV;

- to evaluate PK (by means of population PK) and PK/PD relationships for safety and efficacy of RPV;

- to evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers

**Diagnosis and Main Criteria for Inclusion:** Boys or girls, aged ≥12 to <18 years; weighing ≥32 kg; with documented chronic HIV-1 infection who were aware of their HIV-1 diagnosis (plasma viral load at screening was ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL for Part 1b and Part 2 of the study, and ≥500 HIV-1 RNA copies/mL for Part 1a of the study) and whose screening HIV-1 genotype demonstrated sensitivity to the selected NRTIs; who had, prior to screening, never been treated with a therapeutic HIV vaccine or an HIV drug with the exception of a single dose of nevirapine to prevent mother-to-child transmission; who didn't have any currently active AIDS defining illness (Category C conditions according to the Centers for Disease Control and Prevention [CDC] Classification System for HIV-Infection 1993), any documented genotypic evidence of non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance, any active clinically significant disease (eg, pancreatitis, cardiac dysfunction, active and significant psychiatric disorders, clinical suspicion of adrenal insufficiency, hepatic impairment), active tuberculosis or being treated for tuberculosis at screening or findings during screening or medical history that, in the investigator's opinion, compromised the outcome of the study. Pregnant or breastfeeding girls were excluded. Heterosexually active boys or girls of childbearing potential had to make use of effective birth control methods from screening onwards until at least 30 days after last intake of RPV.

**SUMMARY OF RESULTS:**

**Subject Disposition and Demographics:** In this open-label, single arm study, 71 subjects were screened of whom 36 ART-naive, HIV-1 infected adolescents aged ≥12 to <18 years weighing ≥32 kg were treated with RPV 25 mg qd in combination with an investigator-selected background regimen of 2 NRTIs (intent-to-treat [ITT] population). The study consists of a screening period of maximum 8 weeks, an initial 48-week treatment period, and a post Week 48 treatment extension period of 4 years. This report describes the results of the Week 48 analysis with cut-off date: 12 June 2014.

Of the 36 subjects, 24 (66.7%) subjects were ongoing at the Week 48 analysis cut-off date (see Table 9). Four of the 36 subjects (11.1%) completed the study at Week 48 and did not continue in the post Week 48 extension, while 8/36 (22.2%) subjects prematurely discontinued the study prior to that time. Among the 8 subjects who prematurely discontinued, 6/36 (16.7%) subjects reached a virologic endpoint, 1 (2.8%) subject had a protocol deviation leading to discontinuation, and 1 (2.8%) subject was withdrawn from the study as per tuberculosis withdrawal criteria. Based on pill count, the individual adherence averaged across the study period and was at least 80% for all subjects. Based on the adherence questionnaire only 3/34 (8.8%) subjects indicated to have missed one or more ARV intakes at one or more occasions.

**Table 9 RPV Study C213: Subject Disposition (Intent-to-Treat)**

| Type/Reason/Interval, n (%) | RPV 25 mg qd (N=36) |
|---|---|
| Completed at Week 48 | 4 (11.1%) |
| Discontinued | 8 (22.2%) |
| Adverse event | 1 (2.8%) |
| Up to Week 24 | 1 (2.8%) |
| Other | 1 (2.8%) |
| Up to Week 24 | 1 (2.8%) |
| Subject reached a virologic endpoint | 6 (16.7%) |
| Up to Week 24 | 5 (13.9%) |
| Beyond Week 48 | 1 (2.8%) |
| Ongoing | 24 (66.7%) |

Discontinuation was based on study termination reasons as indicated by the investigator

The majority of subjects were Black or African American (32 subjects; 88.9%) and 20 (55.6%) subjects were female. The median (range) age and weight at screening were 14.5 (12-17) years and 45.2 (33-93) kg, respectively. There were 18 (50.0%) subjects in each of the age groups (≥12 to <15 years and ≥15 to <18 years). For the 20 female subjects, Tanner stage V was seen in 3 (15.0%) girls each for breasts and pubic hair. For the 16 male subjects, Tanner stage V was seen in 2 (12.5%) boys each for pubic hair and genitalia. A total of 14/20 (70.0%) female subjects had had their first menses prior to baseline visit.

The median (range) baseline plasma viral load was 57150.0 (2060-676000) copies/mL. Twenty-eight (77.8%) subjects had a baseline plasma viral load ≤100,000 copies/mL, 6 (16.7%) subjects had a baseline plasma viral load of >100,000 to ≤500,000 copies/mL and 2 (5.6%) subjects had a baseline plasma viral load of >500,000 copies/mL. Note that subjects with a screening plasma viral load of >100,000 copies/mL could be enrolled in Part 1a of the study, and that, by amendment III (29 June 2011), recruitment in Part 1b and Part 2 was limited to subjects with a screening plasma viral load ≤100,000 copies/mL.

Major protocol deviations were observed for 3 (8.3%) subjects. One (2.8%) subject entered the study despite the presence of an exclusionary NNRTI resistance-associated mutation (RAM) at screening. Two other (5.6%) subjects had received an incorrect dose of RPV (ie, several missed intakes), of whom one subject also did not take RPV in accordance with the food requirements prior to the intensive pharmacokinetic visit.

**Efficacy Results:** The analysis of efficacy was performed on the ITT population (N=36). A virologic response of <50 copies/mL (TLOVR) was achieved in 27/36 (75.0%) and 26/36 (72.2%) subjects at Week 24 and Week 48, respectively; 7/36 (19.4%) and 8/36 (22.2%) subjects were considered VF at Week 24 and Week 48, respectively. Of the 8 subjects considered VF per TLOVR (<50 copies/mL) at Week 48, 4 (11.1%) subjects were never suppressed (of whom 1

subject with initial lack of response) and 4 subjects were rebounder. The virologic response rate at Week 24 and Week 48 obtained by FDA Snapshot approach was the same as for TLOVR imputation.

In baseline plasma viral load category ≤100,000 copies/mL (N=28), a virologic response of <50 copies/mL (TLOVR) was achieved in 24/28 (85.7%) and 22/28 (78.6%) subjects at Week 24 and Week 48, respectively. In baseline plasma viral load category >100,000 copies/mL (N = 8), a virologic response of <50 copies/mL (TLOVR) was achieved in 3/8 (37.5%) and 4/8 (50.0%) subjects at Week 24 and Week 48, respectively. For both categories, the virologic response rate at Week 24 and Week 48 obtained by FDA Snapshot approach was the same as for TLOVR imputation.

The median time to virologic response (<50 copies/mL, TLOVR) was 11.4 weeks, and the median time to loss of virologic response (<50 copies/mL, TLOVR) was 156.1 weeks.

To evaluate whether the GCP non-compliance at site [redacted] impacted the results of the study, a sensitivity analysis was performed excluding the data from this site which revealed no major differences with the overall results.

**Table 10. RPV Study C213: Virologic Outcome at Week 24 and Week 48 (<50 copies/mL, TLOVR; Intent-to-Treat)**

| n (%) | RPV 25 mg qd (N=36) | |
|---|---|---|
| | Week 24 | Week 48 |
| Responder | 27 (75.0%) | 26 (72.2%) |
| Virologic failure | 7 (19.4%) | 8 (22.2%) |
| never suppressed | 6 (16.7%) | 4 (11.1%) |
| initial lack of response[a] | 1 (2.8%) | 1 (2.8%) |
| rebounder | 1 (2.8%) | 4 (11.1%) |
| Discontinued due to AE[b] | 1 (2.8%) | 1 (2.8%) |
| Discontinued due to reason other than AE | 1 (2.8%) | 1 (2.8%) |

a Confirmed decrease in plasma viral load of <1.0 log10 at Week 12 from the baseline plasma viral load (ie, 2 consecutive measurements at least 2 weeks apart)
b One subject ([redacted]) discontinued due to an AE of pulmonary tuberculosis (mandatory withdrawal criterion)

The mean (SE) increase in CD4+ cell count from baseline was 147.2 (25.68) cells/μL at Week 24 and 201.2 (32.87) cells/μL at Week 48 (NC=F).

In 5/8 (62.5%) subjects who experienced VF, development of RPV RAMs was observed; the most frequently emerging RPV RAMs in these 5 subjects were E138K (n=4), K101E (n=2) and M230L (n=2). In 3/8 (37.5%) subjects an RPV FC in EC50 >BCO was shown at the last post-baseline visit with genotypic data; these 3 subjects were among the 5 with RPV RAMs. In

4/5 (80.0%) subjects with treatment-emergent RPV RAMs, at least 1 treatment-emergent NRTI RAM was observed at the same time point. These were M184V (n=3), K65R (n=1), and Y115F (n=1).

**Pharmacokinetics Results:**

**Table 11. RPV Study C213: PK Results of RPV After Multiple Dose Administration of RPV 25 mg qd in Adolescents (This Study Part 1) and Adults (Pooled Data of TMC278-C209/C215 PK Substudies)**

| Pharmacokinetics of RPV (mean±SD, $t_{max}$: median [range]) | TMC278-C213 Part 1a (test) | TMC278-C213 Part 1b (test) | TMC278-C213 Part 1a + 1b (test) | TMC278-C209 + TMC278-C215 (reference) |
|---|---|---|---|---|
| N | 11 | 12 | 23 | 44 |
| $C_{trough}$, ng/mL | 68.5 ± 29.0 | 92.1 ± 47.0 | 80.8 ± 40.4 | 67.6 ± 39.0 |
| $C_{min}$, ng/m | 47.0 ±18.1 | 66.4 ± 29.9 | 57.1 ± 26.3 | 53.7 ± 28.3 |
| $C_{max}$, ng/mL | 88.7 ± 25.5 | 127 ± 38.9 | 109 ± 38.0 | 134 ± 72.0 |
| $t_{max}$, h | 5.00 (2.00–9.03) | 5.00 (4.00–6.00) | 5.00 (2.00–9.03) | 4 (1.00–12.00) |
| $AUC_{24h}$, ng.h/mL | 1551 ± 460 | 2167 ± 800 | 1872 ± 717 | 2005 ± 970 |

Pharmacokinetic parameters of the intensive PK visit (Part 1) after intake of RPV 25 mg qd in adolescents (this study Part 1, test) were comparable to those in HIV-infected adults treated with RPV 25 mg qd (reference).

**Table 12. RPV Study C213: Summary of the Statistical Analysis of the Steady-state Pharmacokinetic Parameters of RPV After Multiple Dose Administration of RPV 25 mg qd in Adolescents (This Study Part 1) and in Adults (Pooled Data of TMC278-C209/C215 PK Substudies)**

| | Least Squares Means | | | |
|---|---|---|---|---|
| Parameter | TMC278-C209 + TMC278-C215 (reference) (N = 44) | TMC278-C213 (Part 1a + 1b) (test) (N = 23) | Least Squares Means Ratio, % | 95% Confidence Interval, % |
| $C_{trough}$, ng/mL | 58.3 | 70.6 | 121.07 | 95.45 – 153.58 |
| $C_{min}$, ng/mL | 47.5 | 51.3 | 108.09 | 87.44 – 133.61 |
| $C_{max}$, ng/mL | 116 | 102 | 88.24 | 71.09 – 109.54 |
| $AUC_{24h}$, ng.h/mL | 1782 | 1750 | 98.19 | 80.53 - 119.73 |

The ratio of the least squares (LS) means for adolescents/adults was close to 100% for the different RPV PK parameters. To conclude comparability in RPV pharmacokinetics between adults and adolescents, the adolescents (Part 1)/adults ratio of geometric mean $AUC_{24h}$ needed to be >0.80 and <1.25. This was indeed the case for $AUC_{24h}$, and also for the other PK parameters $C_{trough}$, $C_{min}$ and $C_{max}$.

Based on the population PK analysis (Part 2), the mean (SD) $AUC_{24h}$ and $C_{trough}$ were also comparable in adolescents (2391 [991] ng.h/ml and 84 [39] ng/ml, respectively) and adults (2397 [1032] ng.h/ml and 80 [37] ng/ml, respectively).

PK/EFFICACY: There was no clear relationship with RPV PK and efficacy.

PK/SAFETY: No clear relationship was observed between RPV PK and the occurrence of AEs of interest, changes in laboratory parameters of interest or changes in ECG parameters of interest.

**Safety Results:** For 35 (97.2%) subjects at least 1 AE was reported, for 13 (36.1%) subjects an AE was considered to be at least possibly related to RPV by the investigator. Adverse events were most frequently reported in the following SOCs: infections and infestations (29 [80.6%] subjects), gastrointestinal disorders (15 [41.7%] subjects), investigations (14 [38.9%] subjects) and nervous system disorders (13 [36.1%] subjects). The most frequently reported AEs were influenza, in 15 (41.7%) subjects, upper respiratory tract infection and cough, each in 8 (22.2%) subjects, and decreased blood cortisol, depression and headache, each in 7 (19.4%) subjects. The most frequently reported AEs assessed as at least possibly related to RPV by the investigator were somnolence in 5 (13.9%) subjects and blood cortisol decreased in 3 (8.3%) subjects.

In most subjects, AEs were DAIDS grade 1 or 2 in severity. In total 7 (19.4%) subjects had grade 3 or 4 AEs. The most frequently reported grade 3 or 4 AEs (>1 subject) were malaria and depression in 2 (5.6%) subjects each. None of the grade 3 or 4 AEs were reported as at least possibly related to RPV by the investigator.

An AE summary table is provided in Table 13.

**Table 13. RPV Study C213: Adverse Event Summary Table (Intent-to-Treat)**

| Number of subjects n (%) | RPV 25 mg qd |
|---|---|
| in ITT population | N=36 |
| with at least one AE | 35 (97.2%) |
| with at least one SAE | 6 (16.7%) |
| who died due to an AE | 0 |
| with a DAIDS grade 1 AE or mild AE | 32 (88.9%) |
| with a DAIDS grade 2 AE or moderate AE | 26 (72.2%) |
| with a DAIDS grade 3 AE or severe AE | 5 (13.9%) |
| with a DAIDS grade 4 AE or potentially life-threatening AE | 2 (5.6%) |
| with a DAIDS grade 2, 3 or 4 AE | 28 (77.8%) |
| with a DAIDS grade 3 or 4 AE | 7 (19.4%) |
| with a missing DAIDS grade | 0 |
| with at least one AE for which the study medication was permanently stopped | 1 (2.8%) |
| with at least one AE for which the study medication was temporarily stopped | 0 |
| with an AE which is possibly related to RPV | 7 (19.4%) |
| with an AE which is possibly related to the underlying ART | 5 (13.9%) |
| with an AE which is probably related to RPV | 5 (13.9%) |
| with an AE which is probably related to the underlying ART | 3 (8.3%) |
| with an AE which is very likely related to RPV | 6 (16.7%) |
| with an AE which is very likely related to the underlying ART | 0 |
| with an AE which is possibly, probably or very likely related to RPV | 13 (36.1%) |
| with an AE which is possibly, probably or very likely related to the underlying ART | 7 (19.4%) |
| with an SAE which is possibly, probably or very likely related to RPV | 1 (2.8%) |

No deaths were reported during the study. One (2.8%) subject had 1 AE (pulmonary tuberculosis) for which RPV treatment was stopped and which was not considered related to RPV or ARV regimen by the investigator.

For a total of 6 (16.7%) subjects at least 1 SAE was reported: malaria (2 [5.6%] subjects), lobar pneumonia (1 [2.8%] subject), suicide attempt and suicidal ideation (in the same subject), drug hypersensitivity (1 subject; grade 2 AE, no treatment interruption required), limb abscess (1 subject). All SAEs were considered not or doubtfully related to RPV by the investigator except for drug hypersensitivity which was considered probably related to RPV. The SAE suicide attempt was considered doubtfully related to the ARV regimen by the investigator, all other SAEs were considered not related to the ARV regimen.

To evaluate whether the GCP non-compliance at site [redacted] impacted the results of the study, a sensitivity analysis was performed excluding the data from this site which revealed no major differences with the overall results.

Most of the worst graded laboratory abnormalities were grade 1 or grade 2. Grade 4 creatinine increased, neutrophils and precursors decreased and neutrophils segmented decreased were reported for 1 (2.8%) subject each. Grade 3 amylase increased, neutrophils and precursor decreased, neutrophils segmented decreased were reported in 2 (5.6%) subjects each and grade 3 hypophosphatemia was reported in 1 (2.8%) subject.

The majority of subjects achieved ACTH stimulated cortisol values above the cut-off of 500 nmol/L. At Week 48, 4 subjects had a treatment-emergent abnormal ACTH stimulation test between 450-500 nmol/L and 1 subject had a treatment-emergent abnormal ACTH stimulation test <450 nmol/L. One subject had an abnormal ACTH stimulation test <450 nmol/ at baseline, but achieved an ACTH stimulation test ≥500 nmol/L at Week 48. These changes were considered normal interindividual and intraindividual variability. Small median changes in other endocrinologic parameters were observed. No subject was reported with an AE of adrenal insufficiency.

Mean and median changes from baseline in vital sign and ECG parameters were generally small. None of the median or median changes were considered relevant. Vital signs-related AEs were reported in 4 (11.1%) subjects. As expected in this population, increases in mean and median height, weight and BMI were observed over 48 weeks. In general, there were small increases in mean and median z-scores and percentiles for age-adjusted height, weight and BMI over 48 weeks. For both males and females, increases in Tanner scale could be observed for both pubic hair and genitalia/breasts. Of the 6 female subjects who had not had their first menses prior to baseline, 3 subjects had their first menses during treatment.

**CONCLUSIONS:**

The 48-week efficacy results demonstrate that RPV 25 mg qd, in combination with an investigator selected regimen, is efficacious in adolescents, ≥12 to <18 years of age. A confirmed plasma viral load <50 copies/mL (ITT, TLOVR) was achieved in 27/36 (75.0%) at Week 24 and in 26/36 (72.2%) subjects at Week 48. The proportion of responders was higher in subjects with a baseline plasma viral load ≤100,000 copies/mL (85.7% and 78.6% at Week 24 and Week 48, respectively for <50 copies/mL, TLOVR).

An increase in CD4+ cell counts over the 48-week treatment period was observed.

Based on the resistance analysis, in 5 out of 8 (62.5%) subjects who experienced VF development of RPV RAMs was observed, and 3 out of those 5 (60.0%) subjects experiencing VF with RPV RAMs, showed phenotypic resistance to RPV at the last available visit. In 4/5 (80.0%) subjects who developed RPV RAMs, at least 1 treatment-emergent NRTI RAM was observed at the same time point. The observed treatment-emergent RPV and NRTI RAMs were previously identified in the Phase 3 studies conducted in adults.

The 25 mg qd dose in adolescents resulted in similar RPV exposure as observed in adults.

No apparent relationships were observed between the RPV pharmacokinetics and efficacy or safety parameters at Week 48.

The safety data up to Week 48 demonstrated that RPV, administrated at 25 mg qd, in combination with an investigator-selected background regimen of 2 NRTIs, was generally safe and well tolerated in adolescents. Rilpivirine did not appear to affect pubertal development, including growth, of these adolescents. There were no new relevant safety findings compared with the known RPV safety profile in HIV-1 infected adults.

## 1.2. Overall Extent of Exposure

No data are currently available from studies of FTC/RPV/TAF in HIV-1 infected patients. To date 197 healthy volunteers have received FTC/RPV/TAF in 3 Phase 1 studies.

Since exposures of the FTC and TAF components of the FTC/RPV/TAF FDC have been shown to be bioequivalent to E/C/F/TAF, the safety data for E/C/F/TAF can be extrapolated to the FTC/RPV/TAF FDC. Since exposure of the RPV component of the FTC/RPV/TAF FDC has been shown to be bioequivalent to Edurant, the efficacy data for RPV can be extrapolated to the FTC/RPV/TAF FDC. Therefore, evidence to support the clinical safety of FTC/RPV/TAF is provided by a comprehensive program of 6 clinical studies of E/C/F/TAF, 3 clinical studies of RPV, and 2 clinical studies of the RPV-containing regimen, Complera/Eviplera. The subset of patients receiving FTC/TDF (FTC in combination with a TFV prodrug) within the 2 RPV clinical studies in adults provides data for RPV and FTC administered with a TFV prodrug and, therefore, contains the most relevant data for the FTC/RPV/TAF combination.

In the E/C/F/TAF studies included in this submission, a total of 2486 subjects received at least 1 dose of E/C/F/TAF (150/150/200/10 mg), including 2121 subjects in E/C/F/TAF Phase 3 studies, 273 subjects in the E/C/F/TAF Phase 2 study (including the randomized phase and open-label extension), and 92 subjects in the E/C/F/TAF Phase 1 studies (Table 1 and Table 2).

In the RPV studies included in this submission, a total of 722 subjects received at least 1 dose of RPV (25 mg) including 686 subjects in the RPV Phase 3 studies and 36 subjects in the RPV Phase 2 study (Table 1).

In the Complera/Eviplera studies included in this submission, a total of 518 subjects received at least 1 dose of Complera/Eviplera (200/25/300 mg), including 469 subjects in the Phase 3 study, and 49 subjects in the Phase 2b study (Table 1). Cumulative patient exposure to Complera/Eviplera since first marketing approval in the US on 10 August 2011 to 28 February

2015 is estimated to be 206,654 patient years. The patient exposure is estimated from sales figures and will tend to overestimate exposure, due to accumulation of drug stocks at pharmacies/distributors.

In the other Phase 1 TAF studies, a total of 371 subjects received at least 1 dose of TAF as a single agent or part of another FDC (F/TAF or E/C/F/TAF) (Table 2).

Disposition for subjects in the E/C/F/TAF, RPV, and Complera/Eviplera Phase 2 and Phase 3 studies is described in m2.7.3, Section 3.1.1.

### 1.2.1. E/C/F/TAF Studies

Table 14 presents the duration of exposure to study drug in the E/C/F/TAF Phase 2 and Phase 3 studies. Across the Phase 2 and Phase 3 studies, a total of 2394 subjects have received E/C/F/TAF with a median (Q1, Q3) exposure of 48.1 weeks (42.3, 60.0). The median exposure was similar in subjects who were ART-naive (Studies GS-US-292-0104 and GS-US-292-0111), subjects who were virologically suppressed (Study GS-US-292-0109), and subjects with mild to moderate renal impairment (Study GS-US-292-0112). The median (Q1, Q3) exposure was shorter in adolescent subjects in Study GS-US-292-0106 compared with the studies in adults (12.1 [4.1, 32.1] weeks); however, approximately half of the subjects in the study received E/C/F/TAF for ≥ 24 weeks. In studies with comparators, exposure between groups was similar within each study.

In the open-label extension phase of Study GS-US-292-0102, the median (Q1, Q3) duration of exposure for the E/C/F/TAF group in the All E/C/F/TAF analysis was 105.3 (98.0, 108.1) weeks, with the majority of subjects completing 96 weeks of treatment (92.0%, 103 subjects).

**Table 14. E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Duration of Exposure to Study Drug (Safety Analysis Set)**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 | |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) | Total E/C/F/TAF (N=2233) |
| Total Exposure to Study Drug (weeks) | | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | 959 | 477 | 242 | 6 | 48 | 2394[b] |
| Mean (SD) | 53.6 (12.54) | 52.7 (13.10) | 60.8 (12.94) | 62.0 (9.16) | 46.7 (10.46) | 45.9 (11.79) | 41.7 (11.03) | 42.5 (5.74) | 19.2 (15.14) | 49.4 (17.93)[b] |
| Median | 49.9 | 49.1 | 61.6 | 61.1 | 48.0 | 48.0 | 43.1 | 42.8 | 12.1 | 48.1[b] |
| Q1, Q3 | 47.6, 60.3 | 47.3, 60.3 | 60.0, 66.4 | 60.0, 67.4 | 42.3, 50.3 | 42.1, 50.1 | 36.1, 48.0 | 36.1, 48.1 | 4.1, 32.1 | 42.3, 60.0[b] |
| Min, Max | 0.1, 78.7 | 0.1, 77.1 | 3.3, 76.9 | 25.1, 72.7 | 1.7, 70.4 | 0.3, 65.0 | 4.9, 71.9 | 35.9, 49.4 | 1.0, 60.0 | 0.1, 120.1[b] |
| Total Exposure to Study Drug | | | | | | | | | | |
| >= 4 Weeks (28 days) | 859 (99.2%) | 857 (98.8%) | 111 (99.1%) | 58 (100.0%) | 958 (99.9%) | 472 (99.0%) | 242 (100.0%) | 6 (100.0%) | 44 (91.7%) | 2220 (99.4%) |
| >= 8 Weeks (56 days) | 855 (98.7%) | 854 (98.5%) | 110 (98.2%) | 58 (100.0%) | 958 (99.9%) | 471 (98.7%) | 240 (99.2%) | 6 (100.0%) | 31 (64.6%) | 2200 (98.5%) |
| >= 12 Weeks (84 days) | 853 (98.5%) | 849 (97.9%) | 109 (97.3%) | 58 (100.0%) | 955 (99.6%) | 471 (98.7%) | 235 (97.1%) | 6 (100.0%) | 26 (54.2%) | 2184 (97.8%) |
| >= 16 Weeks (112 days)[c] | 850 (98.2%) | 845 (97.5%) | 107 (95.5%) | 58 (100.0%) | – | – | 233 (96.3%) | 6 (100.0%) | 23 (47.9%) | 1219 (95.7%) |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 | |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) | Total E/C/F/TAF (N=2233) |
| >= 24 Weeks (168 days) | 842 (97.2%) | 832 (96.0%) | 106 (94.6%) | 58 (100.0%) | 919 (95.8%) | 449 (94.1%) | 222 (91.7%) | 6 (100.0%) | 23 (47.9%) | 2118 (94.8%) |
| >= 36 Weeks (252 days)[d] | 830 (95.8%) | 819 (94.5%) | 106 (94.6%) | 57 (98.3%) | 864 (90.1%) | 417 (87.4%) | 189 (78.1%) | 5 (83.3%) | 14 (29.2%) | 2008 (89.9%) |
| >= 48 Weeks (336 days) | 620 (71.6%) | 618 (71.3%) | 105 (93.8%) | 54 (93.1%) | 502 (52.3%) | 239 (50.1%) | 67 (27.7%) | 2 (33.3%) | 1 (2.1%) | 1297 (58.1%) |
| >= 60 Weeks (420 days) | 351 (40.5%) | 328 (37.8%) | 95 (84.8%) | 46 (79.3%) | 158 (16.5%) | 85 (17.8%) | 19 (7.9%) | 0 | 1 (2.1%) | 624 (27.9%) |
| >= 72 Weeks (504 days)[e] | 96 (11.1%) | 91 (10.5%) | 8 (7.1%) | 4 (6.9%) | — | — | — | — | — | — |

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.
If the last dose date was completely missing, or only the year was known, or for subjects still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date; in case of the last study drug end date was nonmissing, then it was used to impute the last dose date.

a Includes subjects in the randomized phase of Study GS-US-292-0102; 161 subjects in the open-label extension are not presented in this column. One hundred three of 112 subjects (92.0%) in the E/C/F/TAF group completed > 96 weeks of treatment with E/C/F/TAF.
b N includes 161 subjects who received E/C/F/TAF in the open-label phase of Study GS-US-292-0102 (53 subjects who switched from STB in the randomized phase and 108 subjects who rolled over from the D/C/F/TAF Phase 2 Study GS-US-299-0102). Descriptive statistics were calculated using N = 2394 that includes these 161 subjects.
c Exposure data for >= 16 weeks were not summarized for Study GS-US-292-0109.
d At 32 weeks (224 days) for Studies GS-US-292-0102 and GS-US-292-0106
e Exposure data for ≥ 72 weeks were not available for Studies GS-US-292-0109, GS-US-292-0112 and GS-US-292-0106

Source: E/C/F/TAF ISS, Tables 4 and Req6863.5; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 7.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 7; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 7; GS-US-292-0106 Interim CSR, Section 15.1, Table 6

### 1.2.2. RPV Studies

**Studies C209 and C215**

A total of 1374 subjects were randomized in the double-blind, active-controlled Phase 3 trials and were included in the Phase 3 Week 96 pooled analysis. Of these, 1368 subjects were treated.

In trial C209, 694 HIV-1 infected, ARV treatment-naive adult subjects were randomized in a 1:1 ratio to receive either oral RPV 25 mg taken once daily or control (EFV 600 mg taken once daily) for 96 weeks, each in combination with a background N(t)RTI regimen containing TDF and FTC. A total of 690 subjects were treated: 346 received RPV and 344 received EFV.

In trial C215, 680 HIV-1 infected, ARV treatment-naive adult subjects were randomized in a 1:1 ratio to receive either oral RPV 25 mg taken once daily or control (EFV 600 mg taken once daily) for 96 weeks, each in combination with a background N(t)RTI regimen containing 2 N(t)RTIs. The investigator-selected N(t)RTIs were either FTC/TDF, zidovudine (AZT)/lamivudine (3TC), or abacavir (ABC)/3TC. A total of 678 subjects were treated: 340 received RPV and 338 received EFV.

Rilpivirine was taken for at least 96 weeks by 566 subjects (82.5%).

Table 15 summarizes treatment duration and exposure in the Phase 3 trials.

**Table 15. RPV Studies C209 and C215: Treatment Duration and Extent of Exposure (Phase 3 Week 96 Pooled Analysis)**

| | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Subject-years of exposure, Sum** | **636.5** | **628.1** | **640.0** | **604.0** | **1276.5** | **1232.1** |
| **Treatment duration (weeks), Median (Range)** | **103.1 (0; 135)** | **103.2 (1; 136)** | **104.4 (2; 133)** | **104.4 (0; 133)** | **104.3 (0; 135)** | **104.1 (0; 136)** |
| **Exposure in weeks, n (%)** | **346 (100)** | **344 (100)** | **340 (100)** | **338 (100)** | **686 (100)** | **682 (100)** |
| < 1 week | 1 (0.3) | 0 | 0 | 6 (1.8) | 1 (0.1) | 6 (0.9) |
| 1 week - 2 weeks | 0 | 3 (0.9) | 0 | 7 (2.1) | 0 | 10 (1.5) |
| 2 weeks - 4 weeks | 1 (0.3) | 8 (2.3) | 1 (0.3) | 5 (1.5) | 2 (0.3) | 13 (1.9) |
| 4 weeks - 12 weeks | 6 (1.7) | 6 (1.7) | 5 (1.5) | 8 (2.4) | 11 (1.6) | 14 (2.1) |
| 12 weeks - 24 weeks | 23 (6.6) | 10 (2.9) | 12 (3.5) | 12 (3.6) | 35 (5.1) | 22 (3.2) |
| 24 weeks - 48 weeks | 9 (2.6) | 20 (5.8) | 16 (4.7) | 9 (2.7) | 25 (3.6) | 29 (4.3) |
| 48 weeks - 96 weeks | 27 (7.8) | 18 (5.2) | 19 (5.6) | 20 (5.9) | 46 (6.7) | 38 (5.6) |
| ≥ 96 weeks | 279 (80.6) | 279 (81.1) | 287 (84.4) | 271 (80.2) | 566 (82.5) | 550 (80.6) |

Source: TMC278-C209-W96-Anal-Gen/Display GEN.13, TMC278-C215-W96-Anal-Gen/Display GEN.13, TMC278-C904-W96-Anal-Gen/Display GEN.13 and Display GEN.15.

### *Studies C209 and C215 (FTC/TDF Subset)*

All subjects in trial C209 received FTC/TDF as their background N(t)RTI regimen. For trial C215, 204 of 340 subjects in the RPV group and 202 of 338 subjects in the control group received FTC/TDF. For both studies overall, 550 of 686 subjects in the RPV group and 546 of 682 subjects in the control group received FTC/TDF.

For the subjects in the FTC/TDF subset, RPV was taken for a total of 96 weeks by 450 subjects (81.8%).

Table 16 summarizes treatment duration and exposure in the FTC/TDF subset in the Phase 3 trials.

**Table 16. RPV Studies C209 and C215 (FTC/TDF Subset): Treatment Duration and Extent of Exposure (Phase 3 Week 96 Pooled Analysis)**

| | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 |
| **Subject-years of exposure, Sum** | **636.5** | **628.1** | **380.6** | **356.3** | **1017.1** | **984.4** |
| **Treatment duration (weeks), Median (Range)** | **103.1 (0; 135)** | **103.2 (1; 136)** | **104.4 (2; 130)** | **104.3 (0.3; 133)** | **104.1 (0.1, 135)** | **103.9 (03, 136)** |
| **Exposure in weeks, n (%)** | **346 (100)** | **344 (100)** | **204 (100)** | **202 (100)** | **550 (100)** | **546 (100)** |
| < 1 week | 1 (0.3) | 0 | 0 | 4 (2.0) | 1 (0.2) | 4 (0.7) |
| 1 week - 2 weeks | 0 | 3 (0.9) | 0 | 6 (3.0) | 0 | 9 (1.6) |
| 2 weeks - 4 weeks | 1 (0.3) | 8 (2.3) | 1 (0.5) | 2 (1.0) | 2 (0.4) | 10 (1.8) |
| 4 weeks - 12 weeks | 6 (1.7) | 6 (1.7) | 2 (1.0) | 6 (3.0) | 8 (1.5) | 12 (2.2) |
| 12 weeks - 24 weeks | 23 (6.6) | 10 (2.9) | 10 (4.9) | 5 (2.5) | 33 (6.0) | 15 (2.7) |
| 24 weeks - 48 weeks | 9 (2.6) | 20 (5.8) | 12 (5.9) | 8 (4.0) | 21 (3.8) | 28 (5.1) |
| 48 weeks - 96 weeks | 27 (7.8) | 18 (5.2) | 8 (3.9%) | 12 (5.9) | 35 (6.4) | 30 (5.5) |
| ≥ 96 weeks | 279 (80.6) | 279 (81.1) | 171 (83.8) | 159 (78.7) | 450 (81.8) | 438 (80.2) |

Treatment duration up to the point of analysis is presented.
Subject-years of exposure = mean treatment duration in weeks x N x 7/365.25
Source: TMC278-C209-W96-Anal-Gen/Display GEN.13, TMC278-C215-W96-Anal-Gen/Display GEN.14, TMC278-C904-W96-Anal-Gen/Display GEN.14 and Display GEN.15.

### Study C213

In C213, a total of 36 ARV treatment-naive, HIV-1 infected adolescents aged ≥12 to <18 years were enrolled and treated with RPV 25 mg qd in combination with an investigator-selected NRTI background regimen (ITT population), the majority of whom (24/36 [66.7%]) were ongoing in the study at the Week 48 analysis cut-off date (see Section 3.1).

At the Week 48 analysis cut-off date, the mean (SD) and median (range) duration of exposure to RPV 25 mg qd was 71.6 (43.09) and 63.50 (1.0-179.0) weeks, respectively. The total patient years of RPV exposure was 49.40. At the Week 48 analysis cut-off date, half of the subjects had reached the Week 64 visit (Table 17).

**Table 17 RPV Study C213: Treatment Duration by Interval (Intent-to-Treat)**

| Interval, n (%) | RPV 25 mg qd (N = 36) |
|---|---|
| 0 - 4 Weeks | 1 (2.8%) |
| 8 - 12 Weeks | 1 (2.8%) |
| 12 - 16 Weeks | 1 (2.8%) |
| 16 - 20 Weeks | 2 (5.6%) |
| 20 - 24 Weeks | 2 (5.6%) |
| 48 - 52 Weeks | 7 (19.4%) |
| 52 - 56 Weeks | 3 (8.3%) |
| 60 - 64 Weeks | 1 (2.8%) |
| 64 - 68 Weeks | 1 (2.8%) |
| 68 - 72 Weeks | 1 (2.8%) |
| 72 - 76 Weeks | 2 (5.6%) |
| 96 - 100 Weeks | 1 (2.8%) |
| 100 - 104 Weeks | 5 (13.9%) |
| 104 - 108 Weeks | 1 (2.8%) |
| 108 - 112 Weeks | 2 (5.6%) |
| 112 - 116 Weeks | 2 (5.6%) |
| 116 - 120 Weeks | 1 (2.8%) |
| 176 - 180 Weeks | 2 (5.6%) |

If a 4-week interval category is not shown, no subject has an exposure within that specific timeframe
Source: TMC278-C213-W48-CSR/Table 14

### 1.2.3. Complera/Eviplera Studies

**Study GS-US-264-0111**

Of the 50 subjects enrolled in the study, 49 received at least 1 dose of study drug. One subject withdrew consent before the start of FTC/RPV/TDF dosing. One subject stopped study medication after 45.4 weeks because of incarceration. All 49 subjects (100%) received study medication for at least 44 weeks; the median (range) length of study drug exposure was 48.0 weeks (45.4, 50.4; GS-US-264-0111, Section 11.1).

**Study GS-US-264-0106**

A total of 469 subjects received at least 1 dose of FTC/RPV/TDF, including 317 subjects in the FTC/RPV/TDF group and 152 subjects in the Delayed Switch group. The mean (SD) duration of exposure to FTC/RPV/TDF was 45.6 (9.21) weeks in the FTC/RPV/TDF group and 23.2 (3.93) weeks in the Delayed Switch group (Table 18).

In the FTC/RPV/TDF group, the percentage of subjects with > 44 weeks of study drug exposure was 91.8%. In the Delayed Switch group, the percentage of subjects with > 20 weeks of study drug exposure was 93.4%.

**Table 18. Complera/Eviplera Study GS-US-264-0106: Exposure to Study Drug (Safety Analysis Set)**

| | FTC/RPV/TDF (N=317) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|
| Duration of Exposure (Weeks)[b, c] | | | |
| Mean (SD) | 45.6 (9.21) | 23.2 (3.93) | 38.3 (13.14) |
| Median | 48.0 | 24.0 | 47.7 |
| Q1, Q3 | 47.7, 48.3 | 23.6, 24.3 | 24.1, 48.1 |
| Min, Max | 0.9, 52.4 | 1.6, 28.1 | 0.9, 52.4 |
| ≥ 1 Day | 317 (100.0%) | 152 (100.0%) | 469 (100.0%) |
| > 4 Weeks | 315 (99.4%) | 151 (99.3%) | 466 (99.4%) |
| > 8 Weeks | 312 (98.4%) | 147 (96.7%) | 459 (97.9%) |
| > 12 Weeks | 307 (96.8%) | 145 (95.4%) | 452 (96.4%) |
| > 16 Weeks | 300 (94.6%) | 143 (94.1%) | 443 (94.5%) |
| > 20 Weeks | 300 (94.6%) | 142 (93.4%) | 442 (94.2%) |
| > 24 Weeks | 298 (94.0%) | 65 (42.8%) | 363 (77.4%) |
| > 28 Weeks | 296 (93.4%) | 1 (0.7%) | 297 (63.3%) |
| > 32 Weeks | 295 (93.1%) | 0 | 295 (62.9%) |
| > 36 Weeks | 294 (92.7%) | 0 | 294 (62.7%) |
| > 40 Weeks | 291 (91.8%) | 0 | 291 (62.0%) |
| > 44 Weeks | 291 (91.8%) | 0 | 291 (62.0%) |
| > 48 Weeks | 150 (47.3%) | 0 | 150 (32.0%) |

Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.
Duration of exposure (weeks) = (last dose date - first dose date + 1) / 7.
Date of last dose is imputed by the Week 48 visit date when the end date is recorded as ongoing on the Study Drug Administration case report form.
Source: GS-US-264-0106 Week 48 CSR, Section 15.1, Table 3.1

## Postmarketing Data

As FTC/RPV/TAF has not been approved, no postmarketing data are available. Relevant postmarketing data for Complera/Eviplera are presented below.

Cumulative patient exposure to Complera/Eviplera since first marketing approval in the US on 10 August 2011 to 28 February 2015 is estimated to be 206,654 patient years. The patient

exposure is estimated from sales figures and will tend to overestimate exposure, due to accumulation of drug stocks at pharmacies/distributors. Postmarketing ADR data are discussed in Section 6.

### 1.2.4. FTC/RPV/TAF Studies

**Study GS-US-366-1159**

Of the 96 total subjects enrolled, 95 subjects received FTC/RPV/TAF (200/25/25 mg), RPV (25-mg), and E/C/F/TAF (150/150/200/10 mg); 1 subject only received E/C/F/TAF (GS-US-366-1159, Section 11.1).

**Study GS-US-366-1651**

A total of 60 subjects received a single dose of FTC/RPV/TAF (200/25/25 mg) under fasted conditions and a single dose of FTC/RPV/TAF (200/25/25 mg) under fed conditions (ie, 2 dosing occasions) (GS-US-366-1651, Section 11.1).

**Study GS-US-366-1689**

A total of 41 of the 42 randomized subjects received 33 days of study drugs. One subject discontinued the study on Day 28 due to an AE after receiving each of the 11 planned study doses of FTC/RPV/TAF and LDV/SOF+FTC/RPV/TAF, and 6 doses of LDV/SOF (GS-US-366-1689, Section 11.1).

## 1.3. Demographic and Other Characteristics of Study Population

### 1.3.1. Summary of Demographic and General Baseline Characteristics

#### 1.3.1.1. E/C/F/TAF Studies

In the Phase 2 and Phase 3 E/C/F/TAF clinical studies, demographic and general baseline characteristics were generally similar between treatment groups within each randomized study (Table 19). The median ages of adult subjects with normal renal function who were ART-naive or virologically suppressed were generally similar (range: 33 to 41 years). Subjects with mild to moderate renal impairment in Study GS-US-292-0112 were older, with a median age of 58 years in Cohort 1 (range: 24 to 82). Across the E/C/F/TAF studies, a total of 97 subjects were ≥ 65 years of age. The median age of adolescent subjects in Study GS-US-292-0106 was 15 years (range: 12 to 17).

Women comprised approximately 15% of the ART-naive population in the E/C/F/TAF pivotal studies (Studies GS-US-292-0104 and GS-US-292-0111), approximately 11% of the virologically suppressed population in Study GS-US-292-0109, approximately 20% of the population with mild to moderate renal impairment in Study GS-US-292-0112. The adolescent study (Study GS-US-292-0106) included 28 female subjects (58.3%). Across the E/C/F/TAF Phase 2 and Phase 3 studies of adult subjects, most subjects were white (range: 56.0% to 69.0%) and black (range: 17.6% to 31.3%), and approximately 15% to 25% subjects were Hispanic or

Latino. Of the adolescent subjects, 87.5% were black and 12.5% were Asian, and none were Hispanic or Latino. The median BMI was generally similar across all studies (approximately 25 $kg/m^2$), except for adolescent subjects in Study GS-US-292-0106 (median [Q1, Q3] BMI 20.0 [18.1, 23.2] $kg/m^2$).

**Table 19. E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Demographic and Baseline Characteristics (Safety Analysis Set)**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Age (Years) | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | 959 | 477 | 242 | 6 | 48 |
| Mean (SD) | 35 (10.4) | 36 (10.7) | 35 (11.3) | 37 (10.6) | 41 (10.1) | 41 (10.1) | 58 (9.9) | 55 (7.1) | 15 (1.9) |
| Median | 33 | 35 | 34 | 38 | 41 | 40 | 58 | 54 | 15 |
| Q1, Q3 | 26, 42 | 28, 44 | 26, 43 | 26, 46 | 33, 48 | 33, 48 | 52, 65 | 49, 59 | 13, 17 |
| Min, Max | 18, 74 | 18, 76 | 18, 71 | 20, 55 | 21, 77 | 22, 69 | 24, 82 | 46, 65 | 12, 17 |
| Sex | | | | | | | | | |
| Male | 733 (84.6%) | 740 (85.4%) | 108 (96.4%) | 57 (98.3%) | 856 (89.3%) | 427 (89.5%) | 192 (79.3%) | 6 (100%) | 20 (41.7%) |
| Female | 133 (15.4%) | 127 (14.6%) | 4 (3.6%) | 1 (1.7%) | 103 (10.7%) | 50 (10.5%) | 50 (20.7%) | 0 | 28 (58.3%) |
| Race | | | | | | | | | |
| American Indian or Alaska Native | 5 (0.6%) | 8 (0.9%) | 0 | 1 (1.7%) | 5 (0.5%) | 2 (0.4%) | 1 (0.4%) | 0 | 0 |
| Asian | 91 (10.5%) | 89 (10.3%) | 3 (2.7%) | 1 (1.7%) | 59 (6.2%) | 35 (7.3%) | 34 (14.0%) | 1 (16.7%) | 6 (12.5%) |
| Black | 223 (25.8%) | 213 (24.6%) | 35 (31.3%) | 16 (27.6%) | 169 (17.6%) | 102 (21.4%) | 44 (18.2%) | 3 (50.0%) | 42 (87.5%) |
| Native Hawaiian or Pacific Islander | 5 (0.6%) | 4 (0.5%) | 0 | 0 | 6 (0.6%) | 1 (0.2%) | 2 (0.8%) | 0 | 0 |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| White | 485 (56.0%) | 498 (57.4%) | 74 (66.1%) | 40 (69.0%) | 651 (67.9%) | 314 (65.8%) | 152 (62.8%) | 2 (33.3%) | 0 |
| Not Permitted | – | – | 0 | 0 | 2 (0.2%) | 1 (0.2%) | 2 (0.8%) | 0 | 0 |
| Other | 57 (6.6%) | 55 (6.3%) | 0 | 0 | 67 (7.0%) | 22 (4.6%) | 7 (2.9%) | 0 | 0 |
| Ethnicity | | | | | | | | | |
| Hispanic or Latino | 167 (19.3%) | 167 (19.3%) | 25 (22.3%) | 11 (19.0%) | 248 (25.9%) | 82 (17.2%) | 31 (12.8%) | 1 (16.7%) | 0 |
| Not Hispanic or Latino | 698 (80.6%) | 698 (80.6%) | 87 (77.7%) | 47 (81.0%) | 709 (73.9%) | 392 (82.2%) | 209 (86.4%) | 5 (83.3%) | 48 (100.0%) |
| Not Permitted | 1 (0.1%) | 1 (0.1%) | 0 | 0 | 2 (0.2%) | 3 (0.6%) | 2 (0.8%) | 0 | 0 |
| Missing | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Region | | | | | | | | | |
| US | 532 (61.4%) | 532 (61.4%) | 109 (97.3%) | 56 (96.6%) | 648 (67.6%) | 316 (66.2%) | 166 (68.6%) | 5 (83.3%) | 9 (18.8%) |
| ex-US | 334 (38.6%) | 335 (38.6%) | 3 (2.7%) | 2 (3.4%) | 311 (32.4%) | 161 (33.8%) | 76 (31.4%) | 1 (16.7%) | 39 (81.3%) |
| Baseline Weight (kg) | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | 959 | 477 | 242 | 6 | 48 |
| Mean (SD) | 77.2 (17.07) | 77.6 (17.09) | 80.4 (13.88) | 79.0 (12.60) | 82.0 (17.67) | 82.7 (18.07) | 70.2 (13.82) | 69.9 (13.22) | 51.9 (13.52) |
| Median | 75.0 | 75.3 | 78.0 | 79.2 | 79.7 | 80.3 | 69.2 | 70.5 | 52.0 |
| Q1, Q3 | 65.0, 86.8 | 65.3, 86.6 | 71.2, 89.3 | 71.2, 86.2 | 70.7, 90.7 | 71.7, 90.7 | 61.2, 78.3 | 56.5, 83.6 | 40.5, 60.5 |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Min, Max | 40.5, 176.0 | 41.7, 152.4 | 56.0, 133.3 | 54.4, 112.5 | 36.2, 218.6 | 43.0, 185.3 | 37.8, 118.4 | 54.0, 84.0 | 35.0, 88.8 |
| Baseline Height (cm) | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | 957 | 476 | 242 | 6 | 48 |
| Mean (SD) | 173.9 (9.46) | 174.2 (9.30) | 175.9 (8.21) | 176.3 (8.19) | 175.4 (9.13) | 175.3 (8.90) | 169.4 (9.22) | 170.8 (6.93) | 157.0 (12.93) |
| Median | 175.3 | 175.3 | 175.3 | 177.8 | 176.0 | 175.7 | 170.1 | 168.9 | 157.3 |
| Q1, Q3 | 169.0, 180.3 | 168.0, 180.3 | 170.2, 182.9 | 172.4, 182.9 | 170.2, 180.3 | 170.0, 180.3 | 164.0, 175.3 | 166.0, 177.8 | 147.2, 166.7 |
| Min, Max | 130.0, 198.1 | 142.2, 198.1 | 149.9, 193.0 | 152.4, 193.0 | 138.0, 204.0 | 142.2, 198.1 | 139.0, 190.5 | 162.6, 180.3 | 122.5, 182.0 |
| Baseline Body Mass Index (kg/m^2) | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | 957 | 476 | 242 | 6 | 48 |
| Mean (SD) | 25.5 (5.23) | 25.5 (5.12) | 26.0 (4.31) | 25.5 (4.41) | 26.6 (5.29) | 26.9 (5.34) | 24.4 (4.12) | 23.9 (4.03) | 20.8 (3.24) |
| Median | 24.4 | 24.5 | 25.6 | 25.1 | 25.8 | 26.1 | 24.1 | 23.6 | 20.0 |
| Q1, Q3 | 22.0, 28.0 | 21.7, 28.0 | 23.1, 28.0 | 22.6, 27.5 | 23.1, 29.1 | 23.1, 29.4 | 21.4, 26.9 | 21.4, 25.7 | 18.1, 23.2 |
| Min, Max | 16.6, 71.0 | 16.6, 54.3 | 17.8, 46.0 | 18.2, 46.9 | 13.4, 65.4 | 16.2, 51.1 | 15.7, 39.8 | 18.6, 30.5 | 16.2, 31.8 |

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. Demographics and baseline characteristics for subjects in the open-label extension are summarized in Study GS-US-292-0102 Week 96 CSR, Section 8.

Source: E/C/F/TAF ISS, Table 2; GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 1.1 and 5.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 1 and 5.1; GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 1 and 4.1; GS-US-292-0106 Interim CSR, Section 15.1, Tables 1 and 4.1

### 1.3.1.2. RPV Studies

**Studies C209 and C215 (FTC/TDF Subset)**

Demographic data for the FTC/TDF subset are shown in Table 20.

**Table 20. RPV Studies C209 and C215 (FTC/TDF Subset): Demographic Characteristics (Phase 3 Week 96 Pooled Analysis)**

| Parameter Specification | C209 | | C215 | | Pooled | | |
|---|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 | Overall N = 1096 |
| **Gender (n [%]), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| Female | 78 (22.5) | 69 (20.1) | 43 (21.1) | 46 (22.8) | 121 (22.0) | 115 (21.1) | 236 (21.5) |
| Male | 268 (77.5) | 275 (79.9) | 161 (78.9) | 156 (77.2) | 429 (78.0) | 431 (78.9) | 860 (78.5) |
| **Age (years)[a], N'** | **346** | **341** | **204** | **202** | **550** | **546** | **1096** |
| Median (Min - Max) | 36.0 (18 - 78) | 36.0 (19 - 67) | 37.0 (20 - 66) | 37.5 (19 - 69) | 36.0 (18 - 78) | 36.0 (19 - 69) | 36.0 (18 - 78) |
| **Body Mass Index ($kg/m^2$), N'** | **345** | **341** | **201** | **200** | **546** | **541** | **1087** |
| Median (Min - Max) | 24.2 (16 - 44) | 23.7 (16 - 42) | 24.1 (16 – 55) | 23.6 (16 – 44) | 24.2 (16 - 55) | 23.6 (16 – 44) | 23.9 (16 – 55) |
| **Race, (n [%]), N'** | **345** | **341** | **204** | **202** | **550** | **546** | **1096** |
| White | 214 (61.8) | 206 (59.9) | 134 (66.3) | 128 (63.4) | 348 (63.5) | 334 (61.2) | 682 (62.3) |
| Black/African American | 89 (25.7) | 80 (23.3) | 45 (22.3) | 48 (23.8) | 134 (24.5) | 128 (23.4) | 262 (23.9) |
| Asian | 33 (9.5) | 48 (14.0) | 21 (10.4) | 22 (10.9) | 54 (9.9) | 70 (12.8) | 124 (11.3) |
| Other | 3 (0.9) | 4 (1.2) | 0 | 3 (1.0) | 3 (0.1) | 7 (1.3) | 10 (0.9) |
| Not allowed to ask per local regulations | 7 (2.0) | 6 (1.7) | 0 | 1 (0.5) | 7 (1.3) | 7 (1.3) | 14 (1.3) |

N = number of subjects per treatment group; N' = number of subjects with data; n = number of observations.

[a] Based on local regulations, German sites were not required to enter day and month of birth, hence the age calculations were not possible for subjects at these sites.

Source: TMC278-C209-W96-Anal-Gen/Display GEN.3, TMC278-C215-W96-Anal-Gen/Display GEN.4, and TMC278-C904-W96-Anal-Gen/Display GEN.4

Demographic characteristics for the FTC/TDF subset were similar in the pooled RPV and control group for all parameters and were similar to those for the overall pooled population. Of all the subjects enrolled in the Phase 3 trials and treated with RPV in the FTC/TDF subset, 78.5% were male and 62.3% were White. The median age was 36 years in both treatment groups. Demographic characteristics for the FTC/TDF subset were similar between the individual Phase 3 trials.

**Study C213**

Subjects were enrolled and treated in the C213 study at sites in the following countries: South Africa (3 sites), India (1 site), Thailand (1 site), USA (1 site), Uganda (1 site).

The majority of subjects were black or African American (32/36 [88.9%] subjects) and 20/36 (55.6%) subjects were female. The median (range) age and weight at screening were 14.5 (12-17) years and 45.2 (33-93) kg, respectively. There were 18 (50.0%) subjects in each of the following age categories: ≥12 to <15 years and ≥15 to <18 years. For the 20 female subjects, Tanner stage V was seen in 3 (15.0%) girls each for breasts and pubic hair. Fourteen (70.0%) of the 20 female subjects had had their first menses prior to baseline visit. For the 16 male subjects, Tanner stage V was seen in 2 (12.5%) boys each for pubic hair and genitalia (TMC278-C213-W48-CSR, Section 4.2).

1.3.1.3. Complera/Eviplera Studies

Summaries of demographic characteristics within Studies GS-US-264-0111 and GS-US-264-0106 are included in m2.7.3, Section 2.3.1.1 and 2.3.1.2, respectively (Summary of Results of Individual Studies). Additional detail is included in the respective CSRs (GS-US-264-0111 CSR and GS-US-264-0106 Week 48 CSR). Brief summaries of demographic characteristics for the 2 studies are provided below.

**Study GS-US-264-0111**

The majority of subjects in the safety analysis set for Study GS-US-264-0111 were male (91.8%), with an overall mean age of 38 years (range, 24 to 57 years); most were white (81.6%) or black (12.2%) and non-Hispanic/Latino (79.6%). The mean value for BMI at baseline was 26.9 $kg/m^2$.

**Study GS-US-264-0106**

Demographic and baseline characteristics in Study GS-US-264-0106 were generally similar between the FTC/RPV/TDF and SBR treatment groups. The majority of subjects were male (87.6%), with an overall mean age of 42 years (range, 19 to 73 years); most were white (76.7%) or black or African American (17.4%) and non-Hispanic/Latino (82.4%). The mean value (SD) for BMI at baseline was 25.9 (5.15) $kg/m^2$.

1.3.1.4. FTC/RPV/TAF Studies

Brief summaries of demographic characteristics for the 3 Phase 1 studies of FTC/RPV/TAF in health volunteers are provided below. Additional detail is included in the respective CSRs.

**Study GS-US-366-1159**

The majority of subjects in the Safety Analysis Set of Study GS-US-366-1159 were male (71.9%) and white (68.8%). At baseline, the median age was 32 years (range: 19 to 45 years). The median (first quartile [Q1], third quartile [Q3]) BMI was 26.4 (23.8, 28.3) $kg/m^2$ (GS-US-366-1159, Section 8.3).

**Study GS-US-366-1651**

The majority of subjects in the Safety Analysis Set of Study GS-US-366-1651were male (60.0%) and white (70.0%). At baseline, the median age was 36 years (range: 18 to 45 years). The median (Q1, Q3) BMI was 26.0 (23.3, 27.3) $kg/m^2$ (GS-US-366-1651, Section 8.3).

**Study GS-US-366-1689**

The majority of subjects in the Safety Analysis Set of Study GS-US-366-1689 were male (71.4%) and white (61.9%). At baseline, the median age was 35years (range: 18 to 45 years). The median (Q1, Q3) BMI was 28.0 (25.9, 28.9) $kg/m^2$ (GS-US-366-1689, Section 8.3).

### 1.3.2. Summary of Baseline Disease Characteristics

#### 1.3.2.1. E/C/F/TAF Studies

In the Phase 2 and Phase 3 E/C/F/TAF studies, baseline disease characteristics were generally similar between treatment groups within each randomized study (Table 21). The median baseline HIV-1 RNA value in ART-naive subjects (across all 5 E/C/F/TAF studies) was approximately 4.5 $log_{10}$ copies/mL, and approximately 25% had baseline HIV-1 RNA > 100,000 copies/mL. Of virologically suppressed subjects in Studies GS-US-292-0109 and GS-US-292-0112, approximately 98% had baseline HIV-1 RNA < 50 copies/mL, and most subjects in the switch groups of Study GS-US-292-0102 also had baseline HIV-1 RNA values < 50 copies/mL (all TDF to TAF: 93.4%; D/C/F/TAF to E/C/F/TAF: 97.1%). Median baseline CD4 cell count was approximately 400 cells/µL in ART-naive subjects (across all 5 E/C/F/TAF studies) and approximately 650 cells/µL in virologically suppressed subjects (Studies GS-US-292-0109 and GS-US-292-0112). The most common HIV risk factor was homosexual sex (approximately 75% to 90%) across subjects who were ART-naive (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102) or virologically suppressed (Study GS-US-292-0109). Heterosexual sex and homosexual sex were approximately equal risk factors (approximately 50% each) for subjects with mild to moderate renal impairment (Study GS-US-292-0112), and vertical transmission was the most common HIV risk factor (66.7%) for adolescent subjects (Study GS-US-292-0106). Most subjects in each study had asymptomatic HIV-1 infection (approximately 75% to 90%; status was not collected at baseline in Study GS-US-292-0109).

The median baseline $eGFR_{CG}$ value was generally similar across ART-naive and virologically suppressed adult subjects (range: 105.7 to 117.0 mL/min). In subjects with mild to moderate renal impairment, the median (Q1, Q3) $eGFR_{CG}$ value was 55.6 (45.7, 62.4) mL/min among subjects who were virologically suppressed at baseline and 60.2 mL/min (45.0, 63.2) among subjects who were ART-naive. In ART-naive adolescent subjects, the median (Q1, Q3) eGFR calculated using the modified Schwartz formula was 110.9 (95.8, 118.8) mL/min/1.73 $m^2$.

Across the Phase 3 studies in adults with normal renal function, most subjects (>89%) had no proteinuria at baseline. In subjects with mild to moderate renal impairment, 9.5% of virologically suppressed subjects had Grade 2 proteinuria at baseline, and 23.1% of subjects had Grade 1 proteinuria at baseline. Among adolescent subjects, < 5% had proteinuria at baseline.

**Table 21. E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Baseline Disease Characteristics (Safety Analysis Set)**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| HIV-1 RNA ($log_{10}$ copies/mL) | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | — | — | 242 | 6 | 48 |
| Mean (SD) | 4.54 (0.665) | 4.53 (0.682) | 4.63 (0.572) | 4.69 (0.577) | — | — | 1.32 (0.318) | 4.66 (0.675) | 4.62 (0.593) |
| Median | 4.58 | 4.58 | 4.55 | 4.58 | — | — | 1.28 | 4.72 | 4.65 |
| Q1, Q3 | 4.14, 4.95 | 4.15, 4.96 | 4.30, 4.89 | 4.35, 5.08 | — | — | 1.28, 1.28 | 4.01, 5.35 | 4.24, 4.94 |
| Min, Max | 2.57, 6.89 | 1.28, 6.98 | 3.11, 6.94 | 3.50, 6.44 | — | — | 1.28, 4.88 | 3.76, 5.39 | 3.25, 6.50 |
| HIV-1 RNA Categories (copies/mL) | | | | | | | | | |
| <= 100,000 | 670 (77.4%) | 672 (77.5%) | 93 (83.0%) | 42 (72.4%) | — | — | 242 (100%) | 4 (66.7%) | 38 (79.2%) |
| > 100,000 to <= 400,000 | 147 (17.0%) | 154 (17.8%) | 14 (12.5%) | 13 (22.4%) | — | — | 0 | 2 (33.3%) | 10 (20.8%)[b] |
| > 400,000 | 49 (5.7%) | 41 (4.7%) | 5 (4.5%) | 3 (5.2%) | — | — | 0 | 0 | |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| CD4 Cell Count (/uL) | | | | | | | | | |
| N | 865 | 867 | 112 | 58 | 959 | 477 | 242 | 6 | 48 |
| Mean (SD) | 426 (215.6) | 429 (219.6) | 404 (181.6) | 394 (209.6) | 701 (261.8) | 689 (248.0) | 664 (286.4) | 412 (244.0) | 468 (215.4) |
| Median | 404 | 406 | 385 | 397 | 675 | 662 | 632 | 397 | 452 |
| Q1, Q3 | 283, 550 | 291, 542 | 283, 528 | 232, 535 | 520, 833 | 525, 831 | 456, 811 | 184, 673 | 326, 563 |
| Min, Max | 0, 1311 | 1, 1360 | 30, 897 | 2, 866 | 89, 1951 | 79, 1739 | 126, 1813 | 115, 708 | 95, 1110 |
| CD4 Cell Count Categories (/uL) | | | | | | | | | |
| < 50 | 24 (2.8%) | 27 (3.1%) | 2 (1.8%) | 1 (1.7%) | 0 | 0 | 0 | 0 | — |
| >= 50 to < 200 | 88 (10.2%) | 90 (10.4%) | 12 (10.7%) | 10 (17.2%) | 5 (0.5%) | 4 (0.8%) | 5 (2.1%) | 2 (33.3%) | 4 (8.3%)[c] |
| >= 200 to < 350 | 218 (25.2%) | 200 (23.1%) | 32 (28.6%) | 14 (24.1%) | 54 (5.6%) | 25 (5.2%) | 19 (7.9%) | 0 | 9 (18.8%) |
| >= 350 to < 500 | 256 (29.6%) | 284 (32.8%) | 33 (29.5%) | 17 (29.3%) | 151 (15.7%) | 70 (14.7%) | 53 (21.9%) | 2 (33.3%) | 18 (37.5%) |
| >= 500 | 279 (32.3%) | 266 (30.7%) | 33 (29.5%) | 16 (27.6%) | 749 (78.1%) | 378 (79.2%) | 165 (68.2%) | 2 (33.3%) | 17 (35.4%) |
| Missing | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Mode of Infection (HIV Risk Factors) | | | | | | | | | |
| Heterosexual Sex | 210 (24.2%) | 219 (25.3%) | 16 (14.3%) | 7 (12.1%) | 216 (22.5%) | 101 (21.2%) | 99 (40.9%) | 3 (50.0%) | 10 (20.8%) |
| Homosexual Sex | 652 (75.3%) | 645 (74.4%) | 100 (89.3%) | 51 (87.9%) | 753 (78.5%) | 375 (78.6%) | 126 (52.1%) | 3 (50.0%) | 6 (12.5%) |
| Intravenous Drug Use | 5 (0.6%) | 6 (0.7%) | 0 | 1 (1.7%) | 9 (0.9%) | 5 (1.0%) | 2 (0.8%) | 0 | 1 (2.1%) |
| Transfusion | 2 (0.2%) | 6 (0.7%) | 0 | 0 | 2 (0.2%) | 2 (0.4%) | 5 (2.1%) | 0 | 0 |
| Vertical Transmission | 2 (0.2%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 32 (66.7%) |
| Unknown | 18 (2.1%) | 27 (3.1%) | 0 | 1 (1.7%) | 17 (1.8%) | 12 (2.5%) | 13 (5.4%) | 0 | 2 (4.2%) |
| Other | 18 (2.1%) | 9 (1.0%) | 1 (0.9%) | 0 | 8 (0.8%) | 7 (1.5%) | 2 (0.8%) | 0 | 0 |
| HIV Disease Status[e] | | | | | | | | | |
| Asymptomatic | 780 (90.4%) | 802 (92.9%) | 99 (88.4%) | 52 (89.7%) | — | — | 180 (74.4%) | 5 (83.3%) | 40 (83.3%) |
| Symptomatic HIV Infection | 53 (6.1%) | 35 (4.1%) | 9 (8.0%) | 5 (8.6%) | — | — | 28 (11.6%) | 1 (16.7%) | 8 (16.7%) |
| AIDS | 30 (3.5%) | 26 (3.0%) | 4 (3.6%) | 1 (1.7%) | — | — | 34 (14.0%) | 0 | 0 |
| Unknown | 3 | 4 | 0 | 0 | — | — | 0 | 0 | 0 |
| $eGFR_{CG}$ (mL/min) | | | | | | | | | |
| N | 866 | 867 | 112 | 58 | 959 | 477 | 242 | 6 | 47 |
| Mean (SD) | 120.8 (30.87) | 118.7 (30.73) | 120.4 (30.77) | 114.8 (23.72) | 111.9 (33.39) | 112.1 (32.70) | 54.8 (11.64) | 55.1 (11.73) | 109.1 (17.18)[d] |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Median | 117.0 | 113.9 | 115.2 | 113.3 | 105.7 | 107.7 | 55.6 | 60.2 | 110.9[d] |
| Q1, Q3 | 99.6, 135.6 | 99.0, 133.6 | 100.8, 131.7 | 97.7, 129.4 | 89.4, 126.0 | 88.7, 128.2 | 45.7, 62.4 | 45.0, 63.2 | 95.8, 118.8[d] |
| Min, Max | 33.7, 287.2 | 55.3, 320.2 | 72.6, 239.5 | 73.5, 176.8 | 48.0, 344.1 | 53.7, 304.8 | 26.2, 89.7 | 36.3, 65.5 | 77.5, 146.1[d] |
| Proteinuria by Urinalysis | | | | | | | | | |
| Grade 0 | 778 (89.8%) | 780 (90.1%) | 101 (90.2%) | 55 (94.8%) | 873 (91.1%) | 430 (90.1%) | 163 (67.4%) | 5 (83.3%) | 46 (95.8%) |
| Grade 1 | 80 (9.2%) | 67 (7.7%) | 10 (8.9%) | 2 (3.4%) | 81 (8.5%) | 44 (9.2%) | 56 (23.1%) | 0 | 1 (2.1%) |
| Grade 2 | 8 (0.9%) | 18 (2.1%) | 1 (0.9%) | 1 (1.7%) | 4 (0.4%) | 3 (0.6%) | 23 (9.5%) | 1 (16.7%) | 1 (2.1%) |
| Grade 3 | 0 | 1 (0.1%) | | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 1 | | 0 | 1 | 0 | 0 | 0 | 0 |
| Diabetes Mellitus[e] | | | | | | | | | |
| Yes | 25 (2.9%) | 40 (4.6%) | 5 (4.5%) | 1 (1.7%) | — | — | 33 (13.6%) | 0 | NA[f] |
| No | 841 (97.1%) | 827 (95.4%) | 107 (95.5%) | 57 (98.3%) | — | — | 209 (86.4%) | 6 (100%) | NA[f] |
| Hypertension[e] | | | | | | | | | |
| Yes | 118 (13.6%) | 146 (16.8%) | 14 (12.5%) | 6 (10.3%) | — | — | 95 (39.3%) | 3 (50%) | NA[f] |
| No | 748 (86.4%) | 721 (83.2%) | 98 (87.5%) | 52 (89.7%) | — | — | 147 (60.7%) | 3 (50%) | NA[f] |
| Cardiovascular Disease[e] | | | | | | | | | |
| Yes | 11 (1.3%) | 14 (1.6%) | 4 (3.6%) | 1 (1.7%) | — | — | — | — | NA[f] |
| No | 855 (98.7%) | 853 (98.4%) | 108 (96.4%) | 57 (98.3%) | — | — | — | — | NA[f] |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Hyperlipidemia[e] | | | | | | | | | |
| Yes | 92 (10.6%) | 100 (11.5%) | 15 (13.4%) | 6 (10.3%) | — | — | — | — | NA[f] |
| No | 774 (89.4%) | 767 (88.5%) | 97 (86.6%) | 52 (89.7%) | — | — | — | — | NA[f] |

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
Medical history characteristics (diabetes mellitus, hypertension, cardiovascular disease and hyperlipidemia) were determined by past medical history.

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. Baseline disease characteristics for subjects in the open-label extension are summarized in Study GS-US-292-0102 Week 96 CSR, Section 8.
b HIV-1 RNA >100,000 copies/mL for Study GS-US-292-0106
c CD4 cell count category of < 200/µL for Study GS-US-292-0106
d eGFR calculated using modified Schwartz formula (mL/min/1.73 $m^2$ for Study GS-US-292-0106
e Medical history data were presented in the original studies from which subjects were rolled over and were not summarized for Study GS-US-292-0109.
f Patients with diabetes, uncontrolled cardiac illness, and uncontrolled illness were excluded from Study GS-US-292-0106.

Source: E/C/F/TAF ISS, Table 3; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 6.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 6.1; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 5.1; GS-US-292-0106 Interim CSR, Section 15.1, Table 5.1

### 1.3.2.2. RPV Studies

**Studies C209 and C215 (FTC/TDF Subset)**

Baseline disease characteristics for the FTC/TDF subset are shown in Table 22.

**Table 22. RPV Studies C209 and C215 (FTC/TDF Subset): Baseline Disease Characteristics (Phase 3 Week 96 Pooled Analysis)**

| Baseline Disease Characteristics | C209 | | C215 | | Pooled | | |
|---|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 | Overall N = 1096 |
| **Viral load[a] (copies/mL), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| Median (Min - Max)[a] | 94950.0 (156 - 3300000) | 105000.0 (1010 - 3360000) | 90700.0 (1480 - 20800000) | 120000.0 (1140 - 2830000) | 93850.0 (156 - 20800000) | 109000.0 (1010 - 3360000) | 102000.0 (156 - 20800000) |
| **Categorized viral load at baseline, (n [%]), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| ≤ 100,000 copies/mL | 181 (52.3) | 163 (47.4) | 107 (52.5%) | 92 (45.5%) | 288 (52.4%) | 255 (46.7%) | 543 (49.5%) |
| > 100,000 to ≤ 500,000 copies/mL | 131 (37.9) | 134 (39.0) | 78 (38.2) | 85 (42.1) | 209 (38.0) | 219 (40.1) | 428 (39.1) |
| > 500,000 copies/mL | 34 (9.8) | 47 (13.7) | 19 (9.3) | 25 (12.4) | 53 (9.6) | 72 (13.2) | 125 (11.4) |
| **$Log_{10}$ viral load, (copies/mL), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| Median (Min - Max) | 5.0 (2 - 7) | 5.0 (3 - 7) | 5.0 (3 – 7) | 5.0 (3 – 6) | 5.0 (2 – 7) | 5.0 (3 – 7) | 5.0 (2 – 7) |
| **Absolute CD4 cell count (cells/µL), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| Median (Min - Max) | 240.0 (1 - 888) | 257.0 (1 - 757) | 267.0 (2 – 744) | 271.5 (1 - 857) | 247.0 (1 – 888) | 261.0 (1 – 857) | 255.0 (1 – 888) |
| **Relative CD4 cell count (%), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| Median (Min - Max) | 18.7 (0 - 42) | 17.8 (0 - 43) | 18.0 (0 – 45) | 16.9 (0 – 41) | 18.4 (0 – 45) | 17.5 (0 – 43) | 17.9 (0 – 45) |
| **Duration of known HIV infection at screening (years), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| Median (Min - Max) | 1.2 (0 - 22) | 1.2 (0 - 25) | 1.8 (0 – 24) | 1.4 (0 – 20) | 1.3 (0 – 24) | 1.30 (0 – 25) | 1.3 (0 – 25) |

| Baseline Disease Characteristics | C209 | | C215 | | Pooled | | |
|---|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 | Overall N = 1096 |
| **Clinical stage of HIV infection at screening (n [%]), N'** | **346** | **344** | **204** | **202** | **550** | **546** | **1096** |
| CDC Category A | 248 (71.7) | 242 (70.3) | 141 (69.1) | 139 (68.8) | 389 (70.7) | 381 (69.8) | 770 (70.3) |
| CDC Category B | 84 (24.3) | 79 (23.0) | 48 (23.5) | 51 (25.2) | 132 (24.0) | 130 (23.8) | 262 (23.9) |
| CDC Category C | 14 (4.0) | 23 (6.7) | 15 (7.4) | 12 (5.9) | 29 (5.3) | 35 (6.4) | 64 (5.8) |

Note: percentages are based on the number of subjects with assessments.

[a] Screening criteria required subjects to have a viral load ≥ 5000 HIV-1 RNA copies/mL. The subjects represented by the lower end of the range are subjects who had the required level at screening, but whose viral load fell to < 5000 HIV-1 RNA copies/mL thereafter. Values above the upper limit of quantification are imputed as 10,000,001. Values below the detection limit are imputed as 47. If the baseline value is missing then the screening value was used.

Source: TMC278-C209-W96-Anal-Gen/Display GEN.5, TMC278-C215-W96-Anal-Gen/Display GEN.6 and TMC278-C904-W96-Anal-Gen/Display GEN.6.

In general, the baseline disease characteristics of the Phase 3 Week 96 pooled trial population FTC/TDF subset were representative of an HIV-infected ARV treatment-naive adult population, and were well balanced between treatment groups. The baseline disease characteristics for the FTC/TDF subset were similar to those for the overall population.

In the RPV group for the FTC/TDF subset, the median baseline viral load was 5.0 $\log_{10}$ copies/mL and the overall median baseline absolute CD4 cell count was 255.0 cells/µL.

At screening, 70.7% of the RPV-treated subjects in the FTC/TDF subset overall had a CDC category A HIV-1 infection, 24.0% had a CDC category B HIV-1 infection and the remaining 5.3% had a CDC category C HIV-1 infection.

The median duration of known HIV infection was 1.3 years in the RPV and control groups.

**Study C213**

Thirty out of 36 (83.3%) subjects had been infected by mother-to-child transmission, while 4/36 (11.1%) subjects were infected by heterosexual contact, 1/36 (2.8%) subject by "other" cause and 1/36 (2.8%) subject by "unknown" cause.

The median (range) baseline viral load was 57150.0 (2060-676000) copies/mL. Twenty-eight of the 36 (77.8%) subjects had a baseline viral load ≤100,000 copies/mL, 6/36 (16.7%) subjects had a baseline viral load of >100,000 to ≤500,000 copies/mL and 2/36 (5.6%) subjects had a baseline viral load of >500,000 copies/mL. Subjects with a screening viral load of >100,000 copies/mL were allowed to be enrolled in Part 1a of the study only.

The mean (SD) and median (range) absolute baseline CD4+ cell count were 426.6 (215.11) cells/µL and 414.0 (25-983) cells/µL, respectively.

The majority of subjects were infected with HIV-1 clade C (23/36 [63.9%] subjects), followed by clade A1 (9/36 [25.0%] subjects). Other clades were reported in at most 2/36 (5.6%) subjects. In adolescents ≥13 years (31 subjects), the HIV-infection at screening was classified as CDC category A in the majority of subjects (23 [74.2%] subjects). In adolescents <13 years (5 subjects), the HIV-infection at screening was classified as sponsor defined category N in 3/5 (60.0%) subjects. The majority of subjects were infected with HIV-1 clade C.

All subjects received RPV 25 mg qd in combination with an investigator-selected background regimen containing 2 NRTIs. The allowed NRTIs were AZT, ABC, or TDF in combination with 3TC or FTC. The combination of NRTIs most frequently used together with RPV was FTC/TDF (24/36 [66.7%] subjects). TDF/3TC was used by 8/36 (22.2%) subjects and AZT/3TC was used by 4/36 (11.1%) subjects (TMC278-C213-W48-CSR/Section 4.3).

1.3.2.3. Complera/Eviplera Studies

Summaries of baseline characteristics within Studies GS-US-264-0111 and GS-US-264-0106 are included in m2.7.3, Section 2.3.1.1 and 2.3.1.2, respectively (Summary of Results of Individual Studies). Additional detail is included in the respective CSRs (GS-US-264-0111 CSR and

GS-US-264-0106 Week 48 CSR). Brief summaries of baseline characteristics for the 2 studies are provided below.

**Study GS-US-264-0111**

At baseline, mean CD4+ cell count was 656 cells/μL (range, 188 to 1528 cells/μL), and the majority of subjects (38 subjects; 77.6%) had a CD4+ cell count of > 500 cells/μL. A total of 47 subjects (95.9%) had an HIV-1 RNA value of < 50 copies/mL (undetectable) at baseline; the remaining 2 subjects had baseline HIV-1 RNA values between 50 and < 400 copies/mL. Both subjects had HIV-1 RNA values of < 50 copies/mL at screening, and both had HIV-1 RNA < 50 copies/mL at all subsequent visits. The mean time since first taking ARV medication (EFV/FTC/TDF) was 2.7 years (range, 0.5 to 7.5 years). (According to the study protocol, subjects' baseline regimen was to be their first and only ARV regimen before switching.)

**Study GS-US-264-0106**

Baseline characteristics in Study GS-US-264-0106 were generally similar between the FTC/RPV/TDF and SBR treatment groups. Overall 1.7% of subjects were co-infected with HBV, and 4.4% were co-infected with HCV.

At baseline, mean (SD) CD4+ cell count was 584 cells/μL (244.2 cells/μL) (range, 42 to 1484 cells/μL), and the majority of subjects (283 subjects; 59.5%) had a CD4+ cell count of > 500 cells/μL. One hundred twenty-five subjects (26.3%) had a baseline CD4+ cell count in the range of 351 to ≤ 500 cells/μL, 46 subjects (9.7%) had a CD4+ cell count between 201 and ≤ 350 cells/μL, 20 subjects (4.2%) had a CD4+ cell count in the range of 51 to ≤ 200 cells/μL, and 2 subjects (0.4%) had a CD4+ cell count at or below 50 cells/μL.

All subjects had HIV-1 RNA below 50 copies/mL at screening. At baseline, a total of 451 subjects (94.7%) had an HIV-1 RNA value of < 50 copies/mL (undetectable), 16 subjects (3.4%) had values between 50 and < 200 copies/mL, 2 subjects (0.4%) had values between 200 and < 400 copies/mL, 2 subjects (0.4%) had values between 400 and < 1000 copies/mL, and 5 (1.1%) subjects had values at or above 1000 copies/mL.

The mean time since first taking ARV medication was 3.3 years (range, 0.4 to 21.6 years). Based on enrollment survey data, the most common reason that subjects enrolled in this study was the desire to simplify their current ARV regimen (88.2%).

Similar proportions of subjects in the FTC/RPV/TDF (86 of 317 subjects [27.1%]) and SBR (51 of 159 subjects [32.1%]) groups had at least 1 form of cardiovascular risk at baseline . The most common cardiovascular risks present at baseline were hyperlipidemia (18.5% overall) and hypertension (14.1% overall). Overall 13.9% of subjects were taking lipid-lowering medications at baseline (11.7% in the FTC/RPV/TDF group and 18.2% in the SBR group) .

## 1.4. Analysis Sets

### 1.4.1. E/C/F/TAF Studies

**Safety Analysis Set**

For ART-naive subjects in the E/C/F/TAF studies (GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), the Safety Analysis Set included all subjects who were randomized and received at least 1 dose of study drug (Table 23). For virologically suppressed subjects in Study GS-US-292-0109, data are presented primarily using the Week 48 Safety Analysis Set, which included all subjects who were randomized by 31 October 2013 and received at least 1 dose of study drug. For subjects with mild to moderate renal impairment (Study GS-US-292-0112), data are presented using the Week 48 Safety Analysis Set, which included all subjects who were enrolled on or prior to 15 November 2013 and received at least 1 dose of study drug. For adolescent subjects (Study GS-US-292-0106), data are presented primarily using the Week 24 Safety Analysis Set, which included all subjects who were enrolled by 11 February 2014 and received at least 1 dose of study drug.

The rationale for defining the analysis sets of Studies GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106 by the specified dates was to include the most current data from these subject populations.

Subjects were grouped according to the treatment they actually received.

**DXA Analysis Sets**

For studies in ART-naive subjects (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), virologically suppressed subjects (Study GS-US-292-0109), and subjects with mild to moderate renal impairment (Study GS-US-292-0112) the Hip DXA Analysis Set included all randomized subjects who received at least 1 dose of study drug and had nonmissing baseline hip BMD values. The Spine DXA Analysis Set (all Phase 2 and Phase 3 studies in adults) included all randomized subjects who received at least 1 dose of study drug and had nonmissing baseline spine BMD values.

For adolescent subjects (Study GS-US-292-0106), the Spine DXA Analysis Set included all enrolled subjects who received at least 1 dose of study drug and had nonmissing baseline and at least 1 postbaseline spine BMD values. The TBLH DXA Analysis Set (Study GS-US-292-0106 only) included all enrolled subjects who received at least 1 dose of study drug and had nonmissing baseline and at least 1 postbaseline TBLH BMD values.

For the Hip, Spine, and TBLH DXA Analysis Sets, subjects were grouped according to the treatment they actually received. All data including data collected after the last dose of study drug were used for analysis, unless specified otherwise.

### Other Analysis Sets

In ART-naive subjects in Study GS-US-292-0102, the All E/C/F/TAF Analysis Set included all subjects who received at least 1 dose of double-blinded E/C/F/TAF during the randomized phase and those subjects who received at least 1 dose of open-label E/C/F/TAF during the open-label extension phase. The All E/C/F/TAF Hip DXA Analysis Set included all subjects who had received at least 1 dose of E/C/F/TAF and had nonmissing baseline value for hip BMD. The All E/C/F/TAF Spine DXA Analysis Set included all subjects who had received at least 1 dose of E/C/F/TAF and had nonmissing baseline value for spine BMD.

In virologically suppressed subjects in Study GS-US-292-0109, the EFV-Related Symptom Analysis Set included all subjects who were on ATR at the time of randomization, received at least 1 dose of study drug, and completed EFV related symptom assessments at the baseline visit and at least 1 postbaseline visit. The Ophthalmologic Substudy Analysis Set included all subjects who participated in the ophthalmologic substudy, received at least 1 dose of study drug, and had nonmissing ophthalmologic assessment results for the baseline visit and at least 1 postbaseline visit.

**Table 23. E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Analysis Sets**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF | STB | E/C/F/TAF | STB | E/C/F/TAF | FTC/TDF+ 3rd Agent | ART-Experienced E/C/F/TAF | ART-Naive E/C/F/TAF | E/C/F/TAF |
| Subjects Randomized/Enrolled | 873 | 871 | 113 | 58 | 963 | 480 | 246 | 6 | 48 |
| Subjects in Safety Analysis Set | 866 (99.2%) | 867 (99.5%) | 112 (99.1%) | 58 (100.0%) | 959 (99.6%) | 477 (99.4%) | 242 (100%) | 6 (100%) | 48 (100.0%) |
| Subjects in Hip DXA Analysis Set | 836 (95.8%) | 848 (97.4%) | 103 (91.2%) | 57 (98.3%) | 902 (93.7%) | 452 (94.2%) | 236 (97.5%) | 6 (100%) | — |
| Subjects in Spine DXA Analysis Set | 845 (96.8%) | 850 (97.6%) | 106 (93.8%) | 58 (100.0%) | 912 (94.7%) | 457 (95.2%) | 236 (97.5%) | 6 (100%) | 23 (47.9%) |
| Subjects in TBLH DXA Analysis Set | — | — | — | — | — | — | — | — | 23 (47.9%) |
| Subjects in Efavirenz-Related Symptom Analysis Set | — | — | — | — | 239 (24.8%) | 116 (24.2%) | — | — | — |
| Subjects in Ophthalmologic Substudy Analysis Set | — | — | — | — | 32 (3.3%) | 15 (3.1%) | — | — | — |
| Subjects in All E/C/F/TAF Analysis Set | — | — | 112 | 53[b] | — | — | — | — | — |
| Subjects in All E/C/F/TAF Hip DXA Analysis Set | — | — | 103 (92.0%) | 52 (98.1%)[b] | — | — | — | — | — |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF | STB | E/C/F/TAF | STB | E/C/F/TAF | FTC/TDF+ 3rd Agent | ART-Experienced E/C/F/TAF | ART-Naive E/C/F/TAF | E/C/F/TAF |
| Subjects in All E/C/F/TAF Spine DXA Analysis Set | — | — | 106 (94.6%) | 53 (100.0%)[b] | — | — | — | — | — |

The denominator for percentages is based on the number of subjects in the Randomized Analysis Set.

a Includes subjects in the randomized phase of Study GS-US-292-0102. A total of 266 subjects entered the extension phase of Study GS-US-292-0102 and received E/C/F/TAF, including 158 subjects from this study after completing the 48-week randomized phase (105 of whom continued on E/C/F/TAF and 53 of whom switched from STB to E/C/F/TAF) and 108 virologically suppressed subjects who rolled over from Study US-GS-299-0102.

b Subjects who switched from STB to E/C/F/TAF in the open-label extension. Not presented here are All TDF to TAF, DRV+COBI+TVD to E/C/F/TAF, and D/C/F/TAF to E/C/F/TAF (GS-US-292-0102 Week 96 CSR, Section 15.1, Table 4.1)

Source: E/C/F/TAF ISS, Tables 1, 20.1.2, and 20.2.2; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 4.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 4; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 3; GS-US-292-0106 Interim CSR, Section 15.1, Table 3

### 1.4.2. RPV Studies

**Studies C209 and C215**

For both the C209 and C215 trials and the pooled analyses (including the FTC/TDF subset), the safety analyses were performed on the ITT population.

**Study C213**

Summaries of AEs and other safety data are based on 36 subjects who received at least 1 dose of RPV 25 mg qd, ie, the ITT population. All available safety data were included in the analysis.

### 1.4.3. Complera/Eviplera Studies

All safety analyses were performed using the safety analysis set for both the GS-US-264-0111 and GS-US-264-0106 studies, defined as all subjects who received at least 1 dose of study drug.

### 1.4.4. FTC/RPV/TAF Studies

**Study GS-US-366-1159**

All 96 subjects were included in the Safety Analysis Set.

**Study GS-US-366-1651**

All 60 subjects were included in the FTC, RPV, and TAF Analysis Sets.

**Study GS-US-366-1689**

All 42 randomized subjects (Randomized Analysis Set) received at least 1 dose of assigned study drug and were included in the Safety Analysis Set and PK Analysis Set.

# 2. ADVERSE EVENTS

## 2.1. Analysis of Adverse Events

### 2.1.1. E/C/F/TAF Studies

Table 24 presents an overall summary of AEs for the E/C/F/TAF Phase 2 and Phase 3 studies. The frequency and type of reported AEs were generally similar in ART-naive adults, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescents. Most subjects across all studies reported at least 1 AE. The percentage of subjects reporting any AE was generally as expected for the respective study populations and associated differences between studies in exposure to study drug. The overall incidence of AEs was similar between treatment groups within each randomized study.

Five ART-naive subjects died (E/C/F/TAF 2 subjects, embolic stroke and alcohol poisoning; STB 3 subjects, cardiac arrest, recreational drug and alcohol overdose, and acute myocardial infarction) in Studies GS-US-292-0104 and GS-US-292-0111. Two virologically suppressed subjects in the E/C/F/TAF group of Study GS-US-292-0109 died during the study (1 subject due to septic shock and the other due to Stage 4 lung adenocarcinoma). None of these events were considered by the investigator as related to study drug. No other subject died in any of the Phase 2 or 3 studies.

The incidences of Grade 3 or 4 AEs and of SAEs were low and generally similar across all studies; few of the reported events were considered related to study drugs by the investigator. Within each study, the incidences of Grade 3 or 4 AEs and of SAEs were also generally similar between treatment groups. These events were reported as not related to study drugs in all but 1 subject (Grade 3 diarrhea lasting 1 day) in the E/C/F/TAF group. The percentage of subjects with Grade 3 or 4 AEs and SAEs was similar between treatment groups in the larger Phase 3 data set of ART-naive subjects.

The percentages of subjects who had any AE considered related to study drugs by the investigator were generally similar across studies and within each study except for Study GS-US-292-0109. As expected, among virologically suppressed subjects who were stable on their prior treatment regimen before participating in Study GS-US-292-0109, subjects who switched to open-label E/C/F/TAF had a higher incidence of any AE considered by the investigator as related to study drug (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects). Most of the AEs considered related to study drug were Grade 1. The incidences of AEs related to study drug were lower in both treatment groups in Study GS-US-292-0109 than that in other studies.

Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study.

With longer exposure to study drug in the open-label extension of Study GS-US-292-0102, the AE profile for the E/C/F/TAF group was consistent with that in the randomized phase.

**Table 24. E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Overall Summary of Adverse Events (Safety Analysis Set)**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| Subjects Experiencing Any | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART-Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Adverse Event | 778 (89.8%) | 782 (90.2%) | 107 (95.5%) | 57 (98.3%) | 764 (79.7%) | 368 (77.1%) | 209 (86.4%) | 5 (83.3%) | 39 (81.3%) |
| Grade 2, 3, or 4 Adverse Event | 419 (48.4%) | 380 (43.8%) | 72 (64.3%) | 29 (50.0%) | 389 (40.6%) | 177 (37.1%) | 114 (47.1%) | 3 (50.0%) | 13 (27.1%) |
| Grade 3 or 4 Adverse Event | 71 (8.2%) | 75 (8.7%) | 13 (11.6%) | 3 (5.2%) | 61 (6.4%) | 32 (6.7%) | 18 (7.4%) | 0 | 4 (8.3%) |
| Study-Drug-Related Adverse Event | 342 (39.5%) | 364 (42.0%) | 43 (38.4%) | 19 (32.8%) | 185 (19.3%) | 61 (12.8%) | 62 (25.6%) | 1 (16.7%) | 18 (37.5%) |
| Grade 2, 3, or 4 Study-Drug-Related Adverse Event | 84 (9.7%) | 75 (8.7%) | 9 (8.0%) | 1 (1.7%) | 46 (4.8%) | 20 (4.2%) | 24 (9.9%) | 1 (16.7%) | 2 (4.2%) |
| Grade 3 or 4 Study-Drug-Related Adverse Event | 12 (1.4%) | 9 (1.0%) | 1 (0.9%) | 0 | 3 (0.3%) | 6 (1.3%) | 3 (1.2%) | 0 | 1 (2.1%) |
| Serious Adverse Event | 70 (8.1%) | 59 (6.8%) | 12 (10.7%) | 3 (5.2%) | 42 (4.4%) | 21 (4.4%) | 26 (10.7%) | 0 | 4 (8.3%) |
| Study-Drug-Related Serious Adverse Event | 3 (0.3%) | 2 (0.2%) | 0 | 0 | 0 | 1 (0.2%) | 0 | 0 | 1 (2.1%) |
| Adverse Event Leading to Premature Study Drug Discontinuation | 8 (0.9%) | 13 (1.5%) | 4 (3.6%) | 0 | 9 (0.9%) | 7 (1.5%) | 8 (3.3%) | 0 | 0 |
| Death | 2 (0.2%) | 3 (0.3%) | 0 | 0 | 2 (0.2%) | 0 | 0 | 0 | 0 |

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. The AE profile of subjects in the open-label extension was similar to the AE profile observed in the randomized phase.

Source: E/C/F/TAF ISS, Table 6; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 20.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 21; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 32; GS-US-292-0106 Interim CSR, Section 15.1, Table 14

## 2.1.2. RPV Studies

### Studies C209 and C215 (FTC/TDF Subset)

A summary of the incidence of AEs at Week 96 is presented for the FTC/TDF subset in Table 25.

**Table 25. RPV Studies C209 and C215 (FTC/TDF Subset): Summary of Treatment-Emergent Adverse Events (Phase 3 Week 96 Pooled Analysis)**

| | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| **AE Summary, n (%)** | **RPV N = 346** | **Control N = 344** | **RPV N = 204** | **Control N = 202** | **RPV N = 550** | **Control N = 546** |
| **Treatment duration (weeks) Median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2; 130.3)** | **104.3 (0.3; 133)** | **104.1 (0.1; 135)** | **103.9 (0.3; 136)** |
| **Subject-years of exposure** | **636.5** | **628.1** | **380.6** | **356.3** | **1017.1** | **984.4** |
| **Any AE** | **309 (89.3)** | **323 (93.9)** | **193 (94.6)** | **187 (92.6)** | **502 (91.3)** | **510 (93.4)** |
| **Any Grade 1 or 2 AE** | **307 (88.7)** | **319 (92.7)** | **190 (93.1)** | **183 (90.6)** | **497 (90.4)** | **502 (91.9)** |
| Grade 1 | 288 (83.2) | 299 (86.9) | 173 (84.8) | 169 (83.7) | 461 (83.8) | 468 (85.7) |
| Grade 2 | 188 (54.3) | 217 (63.1) | 123 (60.3) | 113 (55.9) | 311 (56.5) | 330 (60.4) |
| **Any Grade 3 or 4 AE** | **53 (15.3)** | **73 (21.2)** | **31 (15.2)** | **33 (16.3)** | **84 (15.3)** | **106 (19.4)** |
| Grade 3 | 46 (13.3) | 67 (19.5) | 28 (13.7) | 31 (15.3) | 74 (13.5) | 98 (17.9) |
| Grade 4 | 15 (4.3) | 12 (3.5) | 7 (3.4) | 7 (3.5) | 22 (4.0) | 19 (3.5) |
| **Any treatment-related[a] AE** | **150 (43.4)** | **220 (64.0)** | **107 (52.5)** | **133 (65.8)** | **257 (46.7)** | **353 (64.7)** |
| **Any treatment-related[a] AE of at least Grade 2** | **61 (17.6)** | **115 (33.4)** | **33 (16.2)** | **66 (32.7)** | **94 (17.1)** | **181 (33.2)** |
| **Death** | **0** | **3 (0.9)** | **0** | **1 (0.5)** | **0** | **4 (0.7)** |
| **Any SAE[b]** | **34 (9.8)** | **41 (11.9)** | **18 (8.8)** | **20 (9.9)** | **52 (9.5)** | **61 (11.2)** |
| **AE leading to permanent discontinuation** | **11 (3.2)** | **31 (9.0)** | **10 (4.9)** | **16 (7.9)** | **21 (3.8)** | **47 (8.6)** |
| **AE leading to temporary discontinuation** | **14 (4.0)** | **25 (7.3)** | **12 (5.9)** | **11 (5.4)** | **26 (4.7)** | **36 (6.6)** |
| **Any skin event of interest[c]** | **68 (19.7)** | **108 (31.4)** | **44 (21.6)** | **64 (31.7)** | **112 (20.4)** | **172 (31.5)** |
| Rash (grouped term) | 45 (13.0) | 92 (26.7) | 23 (11.3) | 53 (26.2) | 68 (12.4) | 145 (26.6) |
| **Any neuropsychiatric event of interest[c]** | **141 (40.8)** | **200 (58.1)** | **105 (51.5)** | **131 (64.9)** | **246 (44.7)** | **331 (60.6)** |
| Any neurologic event of interest | 85 (24.6) | 150 (43.6) | 68 (33.3) | 103 (51.0) | 153 (27.8) | 253 (46.3) |
| Any psychiatric event of interest | 98 (28.3) | 126 (36.6) | 61 (29.9) | 65 (32.2) | 159 (28.9) | 191 (35.0) |
| **Any hepatic event of interest[c]** | **22 (6.4)** | **31 (9.0)** | **16 (7.8)** | **11 (5.4)** | **38 (6.9)** | **42 (7.7)** |

| AE Summary, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 |
| **Any event of interest potentially related to QTc prolongation[c]** | **1 (0.3)** | **4 (1.2)** | **2 (1.0)** | **5 (2.5)** | **3 (0.5)** | **9 (1.6)** |
| **Any endocrine event of interest[c]** | **24 (6.9)** | **16 (4.7)** | **17 (8.3)** | **14 (6.9)** | **41 (7.5)** | **30 (5.5)** |

[a] Defined as possibly, probably, or very likely related to treatment in the opinion of the investigator.
[b] Includes SAEs with an outcome of death.
[c] AEs of interest were not identified from single relevant SOCs, but were based on selected AE preferred terms from a number of relevant SOCs.
Source: TMC278-C209-W96-Anal-Gen/Display GEN.13, TMC278-C209-W96-Anal-Saf-AE/Display SAF.1 and Display SAF.3; TMC278-C215-W96-Anal-Gen/Display GEN.14, TMC278-C215-W96-Anal-Saf-AE/Display SAF.2; TMC278-C904-W96-Anal-Gen/Display GEN.14, TMC278-C904-W96-Anal-Saf-AE/Display SAF.2 and Display SAF.4

The occurrence rates of AEs, drug-related AEs, SAEs, deaths, Grade 3 to 4 AEs for the subjects in the FTC/TDF subset were similar to those in the overall population. Most AEs were Grade 1 or 2 in severity. Four of the 7 subjects who died during the trials received FTC/TDF; all 4 were in the control group. Similar to the overall population, the proportion of subjects experiencing AEs leading to permanent discontinuation was smaller in the RPV group (3.8%) than in the control group (8.6%) for the FTC/TDF subset.

Adverse events of interest for the subjects in the FTC/TDF subset were similar to those in the overall population. Skin events of interest were reported in a smaller proportion of subjects in the RPV group (20.4%) than in the control group (31.5%), as were neurologic events of interest (27.8% vs 46.3%, respectively) and psychiatric events of interest (28.9% vs 35.0%, respectively). Hepatic and endocrine events of interest were reported for comparable proportions of subjects in each treatment group (≤ 7.7% of subjects in either treatment group). The incidence of events of interest potentially related to QTc prolongation was low overall (0.5% [3 subjects] and 1.6% [9 subjects] in the RPV and control group, respectively).

### Study C213

An overview of AEs is provided in Table 26.

For 35 (97.2%) subjects at least 1 AE was reported, for 13 (36.1%) of these subjects an AE was considered treatment-related. In most subjects, AEs were of grade 1-2 in severity. At least 1 grade 3-4 AE was reported in a total of 7 (19.4%) subjects. One (2.8%) subject had at least 1 AE for which treatment was stopped. For a total of 6 (16.7%) subjects at least 1 SAE was reported and for 1 (2.8%) subject a treatment-related SAE was reported. No deaths were reported during the study.

**Table 26 RPV Study C213: Adverse Events Summary Table (Intent-to-Treat)**

| Number of subjects n (%) | RPV 25 mg qd |
|---|---|
| in intent-to-treat population | 36 |
| with at least one AE | 35 (97.2%) |
| with at least one SAE | 6 (16.7%) |
| who died due to an AE | 0 |
| with a grade 1 AE or mild AE | 32 (88.9%) |
| with a grade 2 AE or moderate AE | 26 (72.2%) |
| with a grade 3 AE or severe AE | 5 (13.9%) |
| with a grade 4 AE or potentially life-threatening AE | 2 (5.6%) |
| with a grade 2-4 AE | 28 (77.8%) |
| with a grade 3-4 AE | 7 (19.4%) |
| with a missing grade | 0 |
| with at least one AE for which the study drug was permanently stopped | 1 (2.8%) |
| with at least one AE for which the study drug was temporarily stopped | 0 |
| with an AE which is possibly, probably or very likely related to RPV | 13 (36.1%) |
| with an AE which is possibly, probably or very likely related to the underlying ARV treatment | 7 (19.4%) |
| with an SAE which is possibly, probably or very likely related to RPV | 1 (2.8%) |

Source: TMC278-C213-W48-CSR/Table 31

### 2.1.3. Complera/Eviplera Studies

Adverse events were analyzed by frequency, severity, seriousness, relationship to study drug, and action taken with study drug. Analysis of data obtained from continued treatment with FTC/RPV/TDF in virologically suppressed, HIV-1 infected subjects for up to 48 weeks in Studies GS-US-264-0111 and GS-US-264-0106 did not reveal adverse reactions or changes in the tolerability profile (frequency, nature, or severity of AEs) inconsistent with the known safety profile of FTC/RPV/TDF.

**Study GS-US-264-0111**

An overall summary of AEs that occurred during Study GS-US-264-0111 is provided in Table 27. Of the 49 subjects in the safety analysis set, 43 (87.8%) experienced AEs.

**Table 27. Complera/Eviplera Study GS-US-264-0111: Overall Summary of Adverse Events (Safety Analysis Set)**

| Adverse Event Category, n (%) | FTC/RPV/TDF (N = 49) |
|---|---|
| Subjects Experiencing Any Treatment-Emergent AE | 43 (87.8%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE | 3 (6.1%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent AE | 21 (42.9%) |
| Subjects Experiencing Any Treatment-Emergent AE Related to Study Drug | 12 (24.5%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE Related to Study Drug | 0 |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent AE Related to Study Drug | 3 (6.1%) |
| Subjects Experiencing Any Treatment-Emergent SAE | 1 (2.0%) |
| Subjects Experiencing Any Treatment-Emergent SAE Related to Study Drug | 0 |
| Subjects Experiencing Any Treatment-Emergent AE That Caused Permanent Discontinuation or Temporary Interruption From Study Drug | 0 |
| Subjects Who Died | 0 |

Source: GS-US-264-0111 CSR, Section 15.1, Table 5.1.1

### Study GS-US-264-0106

An overall summary of treatment-emergent AEs occurring during Study GS-US-264-0106 is provided in Table 28. In the FTC/RPV/TDF group (ie, subjects who started FTC/RPV/TDF therapy at study baseline and continued on study drug for up to 48 weeks), treatment-emergent AEs were reported by 79.8% of subjects during the study. In the SBR group (ie, subjects remaining on baseline ARV regimen for the first 24 weeks after study baseline), treatment-emergent AEs were reported by 57.2% of subjects. After subjects in the SBR group switched to FTC/RPV/TDF at Week 24 (ie, Delayed Switch group [Weeks 24–48]), treatment-emergent AEs were reported by 71.7% of subjects.

The percentage of subjects who reported a treatment-related AE that was considered by the investigator to be related to study drug was similar between the FTC/RPV/TDF group (24.9%) and the Delayed Switch group (23.0%) during 48 and 24 weeks of FTC/RPV/TDF therapy, respectively. The percentage of subjects who reported a treatment-related AE that was considered by the investigator to be related to study drug was lower among the subjects remaining on their current ARV regimen for the first 24 weeks of the study (2.5% in the SBR group).

No subjects died during the study. The proportion of subjects who experienced treatment-emergent SAEs was low and similar between the FTC/RPV/TDF group (5.7%) and the Delayed Switch group (5.9%) during 48 and 24 weeks of FTC/RPV/TDF therapy, respectively. Before switching to FTC/RPV/TDF, 5.0% of subjects in the SBR group experienced treatment-emergent SAEs during the first 24 weeks of the study. Only 3 subjects in the FTC/RPV/TDF group had a treatment-emergent SAE that was considered by the investigator to

be related to study drug. Thirteen subjects permanently discontinued study drug due to treatment-emergent AEs (7 in the FTC/RPV/TDF group and 6 in the Delayed Switch group).

**Table 28. Complera/Eviplera Study GS-US-264-0106: Overall Summary of Adverse Events (Safety Analysis Set)**

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 253 (79.8%) | 91 (57.2%) | 109 (71.7%) | 362 (77.2%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 18 (5.7%) | 11 (6.9%) | 12 (7.9%) | 30 (6.4%) |
| Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event | 138 (43.5%) | 39 (24.5%) | 47 (30.9%) | 185 (39.4%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug | 79 (24.9%) | 4 (2.5%) | 35 (23.0%) | 114 (24.3%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug | 3 (0.9%) | 0 | 4 (2.6%) | 7 (1.5%) |
| Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug | 31 (9.8%) | 1 (0.6%) | 11 (7.2%) | 42 (9.0%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 18 (5.7%) | 8 (5.0%) | 9 (5.9%) | 27 (5.8%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event Related to Study Drug | 3 (0.9%) | 0 | 0 | 3 (0.6%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Permanent Discontinuation of Study Drug | 7 (2.2%) | 0 | 6 (3.9%) | 13 (2.8%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Temporary Interruption of Study Drug | 3 (0.9%) | 0 | 2 (1.3%) | 5 (1.1%) |

Note: Safety Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug. Adverse events are mapped according to MedDRA Version 15.

[a] Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

Table manually constructed based on the following programmed output:
Programming Details: /gf/gf2243/displays/final/code/t-aesm2.sas v9.1 Output file: t-aesm2.rtf1
Source: GS-US-264-0106 Week 48 CSR, Section 15.1, Table 5.1.1

## 2.1.4. FTC/RPV/TAF Studies

Supportive safety data are also provided by Phase 1 studies of FTC/RPV/TAF in healthy volunteers. As AEs reported in these studies were uncommon and mild, no additional safety data (eg, AEs by organ system or syndrome, laboratory evaluations) are summarized in subsequent sections, additional detail is presented in the CSRs.

**Study GS-US-366-1159**

Adverse events were reported in 6 subjects (6.3%) following FTC/RPV/TAF (Treatment A), 10 subjects (10.5%) following RPV (Treatment B), and 8 subjects (8.3%) following E/C/F/TAF (Treatment C). Adverse events that were considered related to study drug by the investigator were reported in no subject following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 4 subjects (4.2%) following E/C/F/TAF.

No deaths, SAEs, or AEs leading to premature study drug discontinuation were reported. All AEs were Grade 1 in severity. Overall, the most frequently reported AEs were constipation (9 subjects [9.4%]), nausea, and headache (6 subjects [6.3%] each). Constipation was reported for 2 subjects (2.1%) following FTC/RPV/TAF, 6 subjects (6.3%) following RPV, and 2 subjects (2.1%) following E/C/F/TAF. Nausea was reported for 1 subject (1.1%) following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 4 subjects (4.2%) following E/C/F/TAF. Headache was reported for 3 subjects (3.2%) following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 2 subjects (2.1%) following E/C/F/TAF (GS-US-366-1159, Section 11.2).

**Study GS-US-366-1651**

Adverse events were reported in 8 of 60 subjects (13.3%) following FTC/RPV/TAF administered under fasted conditions, 1 of 30 subjects (3.3%) following FTC/RPV/TAF administered under fed conditions (moderate-fat food), and 4 of 30 subjects (13.3%) following FTC/RPV/TAF administered under fed conditions (high-calorie, high-fat food).

One subject had AEs that were considered by the investigator as related to study drug (nausea, vomiting, and dizziness); these occurred after dosing on the day of administration of FTC/RPV/TAF under fed conditions (high-calorie, high-fat food), and all resolved on the same day without treatment.

No deaths or SAEs were reported, and no subjects discontinued due to an AE. All AEs were Grade 1 (mild). None of the AEs was reported by more than 1 subject in any treatment group (GS-US-366-1651, Section 11.2).

**Study GS-US-366-1689**

Overall, FTC/RPV/TAF and LDV/SOF were generally well tolerated when administered alone or in combination. There were no Grade 3 or 4 AEs, deaths, SAEs, or pregnancies reported and only 1 subject permanently discontinued any study drug due to an AE (nonserious, Grade 2 colitis).

By treatment group, the most commonly reported (ie, for > 1 subject) AEs in the LDV/SOF group (Treatment A) were diarrhea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects); in the FTC/RPV/TAF group (Treatment B) was constipation (9.5%, 4 subjects); and in the LDV/SOF+FTC/RPV/TAF group (Treatment C) were constipation (4.8%, 2 subjects) and headache (4.8%, 2 subjects).

Five subjects (11.9%) had AEs that were considered by the investigator to be treatment related. AEs considered related to study drug were only reported for > 1 subject following treatment with

LDV/SOF: nausea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects) (GS-US-366-1689, Section 11.2).

## 2.1.5. Common Adverse Events

### 2.1.5.1. Summary of Common Adverse Events

In the E/C/F/TAF Phase 2 and 3 studies, the frequency and type of reported AEs were generally similar in ART-naive adults, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescents. The percentage of subjects reporting any AE was generally similar across studies, with somewhat lower percentages among virologically suppressed subjects in Study GS-US-292-0109 and ART-naive adolescent subjects in Study GS-US-292-0106. A similar percentage of subjects reported any AE between treatment groups.

In the RPV Phase 3 studies, the occurrence rates of AEs, drug-related AEs, SAEs, deaths, Grade 3 to 4 AEs for the subjects in the FTC/TDF subset were similar to those in the overall population. Most AEs were Grade 1 or 2 in severity. Four of the 7 subjects who died during the trials received FTC/TDF; all 4 were in the control group. Similar to the overall population, the proportion of subjects experiencing AEs leading to permanent discontinuation was smaller in the RPV group (3.8%) than in the control group (8.6%) for the FTC/TDF subset. The AE profile in adolescent Study C213 was similar to that in adults.

Analysis of data obtained from continued treatment with FTC/RPV/TDF in virologically suppressed, HIV-1 infected subjects for up to 48 weeks in Studies GS-US-264-0111 and GS-US-264-0106 did not reveal adverse reactions or changes in the tolerability profile (frequency, nature, or severity of AEs) inconsistent with the known safety profile of FTC/RPV/TDF.

### 2.1.5.2. E/C/F/TAF Studies

#### 2.1.5.2.1. ART-Naive Subjects

##### 2.1.5.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Detailed AE results for the Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (GS-US-292-0104 Week 48 CSR, Section 11.2; GS-US-292-0111 Week 48 CSR, Section 11.2). Pooled results for the 2 studies are described below; AEs that occurred in ≥ 5% of subjects in either treatment group during the studies are presented in Table 29.

The AEs by PT reported for ≥ 10% of subjects in either treatment group of Studies GS-US-292-0104 and GS-US-292-0111 were as follows:

- E/C/F/TAF group — diarrhea (17.0%, 147 subjects), nausea (15.2%, 132 subjects), headache (14.3%, 124 subjects), and upper respiratory tract infection (11.4%, 99 subjects)

- STB group — diarrhea (18.9%, 164 subjects), nausea (17.4%, 151 subjects), upper respiratory tract infection (12.6%, 109 subjects), and headache (12.5%, 108 subjects)

**Table 29. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | E/C/F/TAF (N=866) | STB (N=867) |
|---|---|---|
| Number of Subjects Experiencing Any Adverse Event | 778 (89.8%) | 782 (90.2%) |
| Gastrointestinal disorders | 394 (45.5%) | 425 (49.0%) |
| Diarrhoea | 147 (17.0%) | 164 (18.9%) |
| Nausea | 132 (15.2%) | 151 (17.4%) |
| Vomiting | 62 (7.2%) | 54 (6.2%) |
| General disorders and administration site conditions | 181 (20.9%) | 164 (18.9%) |
| Fatigue | 71 (8.2%) | 71 (8.2%) |
| Pyrexia | 45 (5.2%) | 41 (4.7%) |
| Infections and infestations | 503 (58.1%) | 506 (58.4%) |
| Upper respiratory tract infection | 99 (11.4%) | 109 (12.6%) |
| Nasopharyngitis | 78 (9.0%) | 80 (9.2%) |
| Musculoskeletal and connective tissue disorders | 241 (27.8%) | 213 (24.6%) |
| Back pain | 60 (6.9%) | 57 (6.6%) |
| Arthralgia | 61 (7.0%) | 39 (4.5%) |
| Osteopenia | 32 (3.7%) | 44 (5.1%) |
| Nervous system disorders | 218 (25.2%) | 197 (22.7%) |
| Headache | 124 (14.3%) | 108 (12.5%) |
| Dizziness | 44 (5.1%) | 37 (4.3%) |
| Psychiatric disorders | 163 (18.8%) | 174 (20.1%) |
| Insomnia | 57 (6.6%) | 48 (5.5%) |
| Respiratory, thoracic and mediastinal disorders | 158 (18.2%) | 165 (19.0%) |
| Cough | 67 (7.7%) | 60 (6.9%) |
| Oropharyngeal pain | 39 (4.5%) | 47 (5.4%) |
| Skin and subcutaneous tissue disorders | 208 (24.0%) | 210 (24.2%) |
| Rash | 55 (6.4%) | 46 (5.3%) |

Adverse events were coded using MedDRA 17.0.

System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: E/C/F/TAF ISS, Table 7

### Adverse Events by Severity

The majority of the AEs reported in Studies GS-US-292-0104 and GS-US-292-0111 were Grade 1 or 2. Similar percentages of subjects in each treatment group reported any Grade 3 or 4 AEs (E/C/F/TAF 8.2%, 71 subjects; STB 8.7%, 75 subjects) (E/C/F/TAF ISS, Tables 7 and 10).

No individual Grade 3 or 4 AEs were reported for ≥ 1% of subjects in either treatment group.

### Adverse Events Considered Related to Study Drug

Similar percentages of subjects in both treatment groups had any AE considered related to study drugs by the investigator (E/C/F/TAF 39.5%, 342 subjects; STB 42.0%, 364 subjects); any Grade 2, 3, or 4 AE considered related to study drugs by the investigator (E/C/F/TAF 9.7%, 84 subjects; STB 8.7%, 75 subjects); or any Grade 3 or 4 AE considered related to study drugs by the investigator (E/C/F/TAF 1.4%, 12 subjects; STB 1.0%, 9 subjects; Table 24 and Table 30). The AEs considered related to study drugs by the investigator reported for ≥ 5% of subjects in either treatment group were as follows:

- E/C/F/TAF group — nausea (10.4%, 90 subjects), diarrhea (7.2%, 62 subjects), headache (6.0%, 52 subjects), and fatigue (5.0%, 43 subjects)

- STB group — nausea (13.0%, 113 subjects), diarrhea (8.5%, 74 subjects), and headache (5.4%, 47 subjects)

**Table 30. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Adverse Events Related to Study Drug Reported in ≥ 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | E/C/F/TAF (N=866) | STB (N=867) |
|---|---|---|
| Number of Subjects Experiencing Any Study-Drug-Related Adverse Event | 342 (39.5%) | 364 (42.0%) |
| Gastrointestinal disorders | 185 (21.4%) | 224 (25.8%) |
| Nausea | 90 (10.4%) | 113 (13.0%) |
| Diarrhoea | 62 (7.2%) | 74 (8.5%) |
| Flatulence | 19 (2.2%) | 25 (2.9%) |
| Vomiting | 16 (1.8%) | 27 (3.1%) |
| Abdominal distension | 13 (1.5%) | 9 (1.0%) |
| Abdominal pain | 11 (1.3%) | 11 (1.3%) |
| Abdominal pain upper | 9 (1.0%) | 11 (1.3%) |
| General disorders and administration site conditions | 61 (7.0%) | 46 (5.3%) |
| Fatigue | 43 (5.0%) | 35 (4.0%) |
| Metabolism and nutrition disorders | 26 (3.0%) | 17 (2.0%) |
| Decreased appetite | 12 (1.4%) | 9 (1.0%) |
| Musculoskeletal and connective tissue disorders | 29 (3.3%) | 39 (4.5%) |
| Osteopenia | 8 (0.9%) | 17 (2.0%) |
| Nervous system disorders | 97 (11.2%) | 82 (9.5%) |
| Headache | 52 (6.0%) | 47 (5.4%) |
| Dizziness | 26 (3.0%) | 19 (2.2%) |
| Somnolence | 9 (1.0%) | 10 (1.2%) |
| Psychiatric disorders | 47 (5.4%) | 58 (6.7%) |
| Abnormal dreams | 13 (1.5%) | 26 (3.0%) |
| Insomnia | 17 (2.0%) | 14 (1.6%) |
| Renal and urinary disorders | 10 (1.2%) | 20 (2.3%) |
| Proteinuria | 7 (0.8%) | 10 (1.2%) |
| Skin and subcutaneous tissue disorders | 46 (5.3%) | 42 (4.8%) |
| Rash | 13 (1.5%) | 11 (1.3%) |

Adverse events were coded using MedDRA 17.0.
System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: E/C/F/TAF ISS, Table 11

#### 2.1.5.2.1.2. Study GS-US-292-0102

Detailed AE results for the Phase 2 Study GS-US-292-0102 may be found in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.2).

Adverse events that occurred in ≥ 5% of subjects during the randomized phase are presented in Table 31. Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs. The AEs by PT reported for at least 10% of subjects in either treatment group were as follows:

- E/C/F/TAF group — nausea (22.3%, 25 subjects); diarrhea (17.0%, 19 subjects); upper respiratory tract infection and fatigue (both 16.1%, 18 subjects); and depression (10.7%, 12 subjects)

- STB group — upper respiratory tract infection (20.7%, 12 subjects); diarrhea (15.5%, 9 subjects); back pain and headache (both 13.8%, 8 subjects); nausea (12.1%, 7 subjects); and cough (10.3%, 6 subjects)

**Table 31. E/C/F/TAF Study GS-US-292-0102: Treatment Emergent Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a,b] | E/C/F/TAF (N=112) | STB (N=58) |
|---|---|---|
| Number of Subjects Experiencing Any Adverse Event | 107 (95.5%) | 57 (98.3%) |
| Endocrine disorders | 7 (6.3%) | 0 |
| Hypogonadism | 7 (6.3%) | 0 |
| Gastrointestinal disorders | 59 (52.7%) | 28 (48.3%) |
| Nausea | 25 (22.3%) | 7 (12.1%) |
| Diarrhoea | 19 (17.0%) | 9 (15.5%) |
| Vomiting | 9 (8.0%) | 4 (6.9%) |
| Flatulence | 6 (5.4%) | 2 (3.4%) |
| Constipation | 4 (3.6%) | 3 (5.2%) |
| Dyspepsia | 4 (3.6%) | 3 (5.2%) |
| General disorders and administration site conditions | 31 (27.7%) | 9 (15.5%) |
| Fatigue | 18 (16.1%) | 5 (8.6%) |
| Immune system disorders | 5 (4.5%) | 3 (5.2%) |
| Seasonal allergy | 4 (3.6%) | 3 (5.2%) |
| Infections and infestations | 83 (74.1%) | 33 (56.9%) |
| Upper respiratory tract infection | 18 (16.1%) | 12 (20.7%) |
| Pharyngitis | 10 (8.9%) | 2 (3.4%) |
| Bronchitis | 7 (6.3%) | 3 (5.2%) |
| Sinusitis | 7 (6.3%) | 3 (5.2%) |
| Conjunctivitis | 9 (8.0%) | 0 |
| Nasopharyngitis | 7 (6.3%) | 2 (3.4%) |
| Influenza | 8 (7.1%) | 0 |
| Syphilis | 5 (4.5%) | 3 (5.2%) |
| Acarodermatitis | 4 (3.6%) | 3 (5.2%) |
| Musculoskeletal and connective tissue disorders | 30 (26.8%) | 16 (27.6%) |
| Back pain | 3 (2.7%) | 8 (13.8%) |
| Neck pain | 3 (2.7%) | 3 (5.2%) |
| Pain in extremity | 1 (0.9%) | 3 (5.2%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 8 (7.1%) | 8 (13.8%) |
| Anorectal human papilloma virus infection | 6 (5.4%) | 4 (6.9%) |
| Skin papilloma | 0 | 3 (5.2%) |

| Adverse Events by System Organ Class and Preferred Term[a,b] | E/C/F/TAF (N=112) | STB (N=58) |
|---|---|---|
| Nervous system disorders | 23 (20.5%) | 14 (24.1%) |
| Headache | 11 (9.8%) | 8 (13.8%) |
| Paraesthesia | 3 (2.7%) | 4 (6.9%) |
| Psychiatric disorders | 28 (25.0%) | 13 (22.4%) |
| Depression | 12 (10.7%) | 3 (5.2%) |
| Insomnia | 6 (5.4%) | 4 (6.9%) |
| Abnormal dreams | 8 (7.1%) | 1 (1.7%) |
| Anxiety | 4 (3.6%) | 5 (8.6%) |
| Respiratory, thoracic and mediastinal disorders | 26 (23.2%) | 13 (22.4%) |
| Cough | 11 (9.8%) | 6 (10.3%) |
| Skin and subcutaneous tissue disorders | 37 (33.0%) | 15 (25.9%) |
| Rash | 11 (9.8%) | 3 (5.2%) |

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 21.1

### Adverse Events by Severity

The majority of the AEs reported in Study GS-US-292-0102 were Grade 1 or Grade 2.

In the randomized phase, similar percentages of subjects in each group had any Grade 3 AEs (E/C/F/TAF 11.6%, 13 subjects; STB 5.2%, 3 subjects). No Grade 4 AEs were reported in either treatment group. By individual PT, no Grade 3 AE was reported for > 1 subject in either group. One Grade 3 AE of diarrhea lasting 1 day was reported for Subject [redacted] in the E/C/F/TAF group and was considered related to the study drugs by the investigator.

Grade 3 AEs were reported for 17 subjects (15.2%) in the E/C/F/TAF group in the all E/C/F/TAF analysis. No Grade 4 AEs were reported. Blood creatine phosphokinase increased was the only Grade 3 AE reported for 2 subjects (Subjects [redacted] and [redacted]). Both events were nonserious and considered unrelated to the study drugs by the investigator. Neither subject discontinued study drug due to blood creatine phosphokinase increased.

### Adverse Events Considered Related to Study Drug

In the randomized phase, similar percentages of subjects in each group had any AE considered related to the study drugs by the investigator (E/C/F/TAF 38.4%, 43 subjects; STB 32.8%, 19 subjects; Table 32). The most commonly reported AEs considered related to the study drugs by the investigator by PT were as follows: nausea (E/C/F/TAF 12.5%, 14 subjects, STB 8.6%, 5 subjects), diarrhea (E/C/F/TAF 6.3%, 7 subjects; STB 6.9%, 4 subjects), and fatigue (E/C/F/TAF 6.3%, 7 subjects; STB 3.4%, 2 subjects).

**Table 32. E/C/F/TAF Study GS-US-292-0102: Study Drug Related, Treatment Emergent Adverse Events Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term and Highest Severity[a,b] | E/C/F/TAF (N=112) | STB (N=58) |
|---|---|---|
| Number of Subjects Experiencing Any Study-Drug-Related Adverse Event | 43 (38.4%) | 19 (32.8%) |
| Gastrointestinal disorders | 25 (22.3%) | 13 (22.4%) |
| Nausea | 14 (12.5%) | 5 (8.6%) |
| Diarrhoea | 7 (6.3%) | 4 (6.9%) |
| Flatulence | 6 (5.4%) | 2 (3.4%) |
| Constipation | 2 (1.8%) | 1 (1.7%) |
| Abdominal distension | 1 (0.9%) | 1 (1.7%) |
| Abdominal pain | 2 (1.8%) | 0 |
| Dyspepsia | 0 | 2 (3.4%) |
| Vomiting | 2 (1.8%) | 0 |
| Faeces soft | 0 | 1 (1.7%) |
| General disorders and administration site conditions | 8 (7.1%) | 2 (3.4%) |
| Fatigue | 7 (6.3%) | 2 (3.4%) |
| Investigations | 1 (0.9%) | 1 (1.7%) |
| Bone density decreased | 0 | 1 (1.7%) |
| Metabolism and nutrition disorders | 5 (4.5%) | 1 (1.7%) |
| Hyperlipidaemia | 2 (1.8%) | 1 (1.7%) |
| Decreased appetite | 2 (1.8%) | 0 |
| Musculoskeletal and connective tissue disorders | 2 (1.8%) | 2 (3.4%) |
| Osteopenia | 1 (0.9%) | 2 (3.4%) |
| Nervous system disorders | 9 (8.0%) | 1 (1.7%) |
| Headache | 5 (4.5%) | 0 |
| Dysgeusia | 2 (1.8%) | 0 |
| Paraesthesia | 2 (1.8%) | 0 |
| Somnolence | 0 | 1 (1.7%) |
| Psychiatric disorders | 8 (7.1%) | 1 (1.7%) |
| Abnormal dreams | 5 (4.5%) | 1 (1.7%) |
| Depressed mood | 0 | 1 (1.7%) |

| Adverse Events by System Organ Class and Preferred Term and Highest Severity[a,b] | E/C/F/TAF (N=112) | STB (N=58) |
|---|---|---|
| Insomnia | 0 | 1 (1.7%) |
| Skin and subcutaneous tissue disorders | 4 (3.6%) | 1 (1.7%) |
| Night sweats | 2 (1.8%) | 0 |
| Onychoclasis | 0 | 1 (1.7%) |

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 25.1

#### 2.1.5.2.2. Virologically Suppressed Subjects

##### 2.1.5.2.2.1. Study GS-US-292-0109

Detailed AE results for the Phase 3 Study GS-US-292-0109 may be found in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.2).

Adverse events that occurred in ≥ 5% of subjects in Study GS-US-292-0109 are presented in Table 33. Common AEs were consistent with those expected in the subject population, the known safety profiles of the study drugs, and with previous clinical study experience with E/C/F/TAF. The most common AEs (ie, occurred in ≥ 5% of subjects) by treatment group were as follows:

- E/C/F/TAF: Upper respiratory tract infection (12.1%, 116 of 959 subjects), diarrhea (8.0%, 77 subjects), nasopharyngitis (6.7%, 64 subjects), headache (6.0%, 58 subjects), and cough (5.1%, 49 subjects)

- FTC/TDF+3rd Agent: Upper respiratory tract infection (7.5%, 36 of 477 subjects), diarrhea (7.5%, 36 subjects), and nasopharyngitis (5.5%, 26 subjects)

No AE by PT was reported with a difference in percentages of ≥ 5% between groups.

**Table 33. E/C/F/TAF Study GS-US-292-0109: Treatment Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a,b,c] | E/C/F/TAF (N=959) | FTC/TDF+3rd Agent (N=477) |
|---|---|---|
| Number of Subjects Experiencing Any Adverse Event | 764 (79.7%) | 368 (77.1%) |
| Gastrointestinal disorders | 263 (27.4%) | 102 (21.4%) |
| Diarrhoea | 77 (8.0%) | 36 (7.5%) |
| Infections and infestations | 461 (48.1%) | 215 (45.1%) |
| Upper respiratory tract infection | 116 (12.1%) | 36 (7.5%) |
| Nasopharyngitis | 64 (6.7%) | 26 (5.5%) |
| Nervous system disorders | 159 (16.6%) | 50 (10.5%) |
| Headache | 58 (6.0%) | 17 (3.6%) |
| Respiratory, thoracic and mediastinal disorders | 149 (15.5%) | 55 (11.5%) |
| Cough | 49 (5.1%) | 15 (3.1%) |

a Adverse events were coded using MedDRA 17.0.
b System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 22

### Adverse Events by Severity

Most AEs reported in either treatment group were Grade 1 or Grade 2 (Table 24). A similar percentage of subjects in each group had any Grade 3 or Grade 4 AE reported (E/C/F/TAF 6.4%, 61 subjects; FTC/TDF+3rd Agent 6.7%, 32 subjects); most of these events were Grade 3 (E/C/F/TAF 53 subjects; FTC/TDF+3rd Agent 29 subjects).

No Grade 3 or Grade 4 AEs were reported for ≥ 1% of subjects in either group.

### Adverse Events Considered Related to Study Drug

A higher percentage of subjects in the switch group (ie, E/C/F/TAF treatment group) had any AE considered by the investigator as related to study drug (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects, Table 34).

The most common AEs by PT considered by the investigator as related to study drug, reported for ≥ 1% of subjects in either group were as follows:

- E/C/F/TAF: Diarrhea (2.5%, 24 of 959 subjects), nausea (2.2%, 21 subjects), flatulence (1.9%, 18 subjects), headache (1.8%, 17 subjects), abnormal dreams (1.3%, 12 subjects), dizziness (1.1%, 11 subjects), and insomnia (1.0%, 10 subjects)

- FTC/TDF+3rd Agent: Jaundice (1.9%, 9 of 477 subjects), osteopenia (1.3%, 6 subjects), dizziness (1.3%, 6 subjects), abnormal dreams (1.3%, 6 subjects), diarrhea (1.3%, 6 subjects), insomnia (1.3%, 6 subjects), and ocular icterus (1.0%, 5 subjects)

The incidence of common study drug-related AEs were similar for each treatment group. All reports of study drug-related jaundice and ocular icterus were for subjects taking ATV/boosted+TVD regimens.

**Table 34. E/C/F/TAF Study GS-US-292-0109: Study Drug-Related Adverse Events Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a,b,c] | E/C/F/TAF (N=959) | FTC/TDF+3rd Agent (N=477) |
|---|---|---|
| Number of Subjects Experiencing Any Study-Drug-Related Adverse Event | 185 (19.3%) | 61 (12.8%) |
| Eye disorders | 2 (0.2%) | 5 (1.0%) |
| Ocular icterus | 0 | 5 (1.0%) |
| Gastrointestinal disorders | 74 (7.7%) | 11 (2.3%) |
| Diarrhoea | 24 (2.5%) | 6 (1.3%) |
| Nausea | 21 (2.2%) | 2 (0.4%) |
| Flatulence | 18 (1.9%) | 1 (0.2%) |
| Hepatobiliary disorders | 1 (0.1%) | 11 (2.3%) |
| Jaundice | 0 | 9 (1.9%) |
| Musculoskeletal and connective tissue disorders | 19 (2.0%) | 9 (1.9%) |
| Osteopenia | 8 (0.8%) | 6 (1.3%) |
| Nervous system disorders | 44 (4.6%) | 8 (1.7%) |
| Dizziness | 11 (1.1%) | 6 (1.3%) |
| Headache | 17 (1.8%) | 0 |
| Psychiatric disorders | 38 (4.0%) | 9 (1.9%) |
| Abnormal dreams | 12 (1.3%) | 6 (1.3%) |
| Insomnia | 10 (1.0%) | 6 (1.3%) |

a Adverse events were coded using MedDRA 17.0.
b System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 26

#### 2.1.5.2.2.2. Study GS-US-292-0102 Open-Label Extension

In the open-label extension of Phase 2 Study GS-US-292-0102, common AEs among virologically suppressed subjects who switched treatment were consistent with those observed in this subject population and those seen during the randomized phase (Section 2.1.5.2.1.2).

**Adverse Events by Severity**

The percentages of subjects in the switch groups who had Grade 3 or Grade 4 AEs were low (all TDF to TAF 4.4%, 4 of 91 subjects; D/C/F/TAF to E/C/F/TAF 1.4%, 1 of 70 subjects); no Grade 4 AEs were reported in any switch group. By individual PT, no Grade 3 AEs were reported for > 1 subject in any switch group, and none was considered related to the study drugs by the investigator.

**Adverse Events Considered Related to Study Drug**

The percentages of subjects in the switch groups who had study drug related AEs were low. One subject in the all TDF to TAF group had a Grade 2 AE of dyspepsia considered related to study drug by the investigator.

### 2.1.5.2.3. Subjects with Mild to Moderate Renal Impairment

#### 2.1.5.2.3.1. Study GS-US-292-0112

Detailed AE results for the Phase 3 Study GS-US-292-0112 may be found in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.3).

Adverse events that occurred in ≥ 5% of Cohort 1 switch subjects are presented in Table 35. Common AEs were consistent with those expected in the subject population and with the safety profiles seen in subjects with normal renal function. The most commonly reported AEs in Cohort 1 switch subjects were diarrhea (8.7%, 21 subjects), arthralgia (8.3%, 20 subjects), and bronchitis and osteopenia (7.9%, 19 subjects for each AE). Of note, 16 of 19 subjects had the AE of osteopenia reported on Day 1, suggesting that these AEs were most likely reported based on the baseline (predose) DXA scan and not truly treatment emergent.

In Cohort 1 switch subjects, the following AEs were reported for a lower percentage of subjects with baseline $eGFR_{CG}$ < 50 mL/min than with baseline $eGFR_{CG}$ ≥ 50 mL/min: upper respiratory infection (1.3% versus 9.9%); headache (2.5% versus 9.3%); and back pain (2.5% versus 8.0%).

Rates of AEs in general were low despite higher FTC exposures in subjects with baseline $eGFR_{CG}$ < 50 mL/min. Pruritus generalized was reported in 1 subject (1.3%), and pain was reported in 1 subject (1.3%), in Cohort 1 subjects with baseline $eGFR_{CG}$ < 50 mL/min.

No individual AE occurred in > 1 subject in the Cohort 2 ART-naive subjects.

**Table 35. E/C/F/TAF Study GS-US-292-0112: Adverse Events Reported for at Least 5% of Subjects in Cohort 1 (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a,b] | Cohort 1: Switch | | | Cohort 2: ART-Naive |
|---|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) | Total (N = 6) |
| Subjects Experiencing Any Adverse Event | 67 (83.8%) | 142 (87.7%) | 209 (86.4%) | 5 (83.3%) |
| Gastrointestinal Disorders | | | | |
| Diarrhoea | 8 (10.0%) | 13 (8.0%) | 21 (8.7%) | 1 (16.7%) |
| Nausea | 5 (6.3%) | 12 (7.4%) | 17 (7.0%) | 0 |
| General Disorders and Administration Site Conditions | | | | |
| Fatigue | 4 (5.0%) | 10 (6.2%) | 14 (5.8%) | 1 (16.7%) |
| Infections and Infestations | | | | |
| Bronchitis | 7 (8.8%) | 12 (7.4%) | 19 (7.9%) | 0 |
| Upper Respiratory Tract Infection | 1 (1.3%) | 16 (9.9%) | 17 (7.0%) | 1 (16.7%) |
| Musculoskeletal and Connective Tissue Disorders | | | | |
| Arthralgia | 6 (7.5%) | 14 (8.6%) | 20 (8.3%) | 1 (16.7%) |
| Osteopenia | 8 (10.0%) | 11 (6.8%) | 19 (7.9%) | 0 |
| Pain in Extremity | 3 (3.8%) | 13 (8.0%) | 16 (6.6%) | 1 (16.7%) |
| Back Pain | 2 (2.5%) | 13 (8.0%) | 15 (6.2%) | 0 |
| Nervous System Disorders | | | | |
| Headache | 2 (2.5%) | 15 (9.3%) | 17 (7.0%) | 0 |
| Dizziness | 7 (8.8%) | 7 (4.3%) | 14 (5.8%) | 0 |
| Renal and Urinary Disorders | | | | |
| Renal Cyst | 5 (6.3%) | 8 (4.9%) | 13 (5.4%) | 0 |
| Respiratory, Thoracic and Mediastinal Disorders | | | | |
| Cough | 4 (5.0%) | 8 (4.9%) | 12 (5.0%) | 0 |

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Table 33

**Adverse Events by Severity**

The majority of the AEs reported in Study GS-US-292-0112 were Grade 1 or Grade 2.

In Cohort 1 (switch), Grade 3 and 4 AEs were reported for 7.4% of subjects (n = 18): 6.6% of subjects (n = 16) had Grade 3 AEs and 0.8% of subjects (n = 2) had Grade 4 AEs. Myocardial infarction (3 subjects) was the only Grade 3 or 4 AE reported in > 1 subject; each event was serious and considered unrelated to study drug by the investigator. Three subjects had a single nonserious Grade 3 AE considered related to study drug by the investigator: blood creatine phosphokinase increased (baseline $eGFR_{CG}$ < 50 mL/min group), gastroesophageal reflux disease (baseline $eGFR_{CG}$ ≥ 50 mL/min group), and hypercholesterolemia (baseline $eGFR_{CG}$ ≥ 50 mL/min group).

No Grade 3 or 4 AEs were reported for Cohort 2 ART-naive subjects.

**Adverse Events Considered Related to Study Drug**

Adverse events considered related to the study drugs by the investigator that occurred in ≥ 1% of Cohort 1 switch subjects are presented in Table 36. The most commonly reported AEs considered related to the study drugs by the investigator subjects were dizziness (2.9%, 7 subjects), diarrhea (2.5%, 6 subjects), and headache (2.1%, 5 subjects).

One AE considered related to the study drug by the investigator was reported in a Cohort 2 ART-naive subject (hyperlipidemia).

**Table 36. E/C/F/TAF Study GS-US-292-0112: Study Drug Related, Treatment Emergent Adverse Events Reported for at Least 1% of Subjects in Cohort 1 (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a,b] | Cohort 1: Switch | | | Cohort 2: ART-Naive |
|---|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) | Total (N = 6) |
| Subjects Experiencing Any Study Drug-Related Adverse Event | 21 (26.3%) | 41 (25.3%) | 62 (25.6%) | 1 (16.7%) |
| Gastrointestinal Disorders | | | | |
| Diarrhoea | 1 (1.3%) | 5 (3.1%) | 6 (2.5%) | 0 |
| Constipation | 1 (1.3%) | 3 (1.9%) | 4 (1.7%) | 0 |
| Flatulence | 2 (2.5%) | 2 (1.2%) | 4 (1.7%) | 0 |
| Nausea | 1 (1.3%) | 3 (1.9%) | 4 (1.7%) | 0 |
| Abdominal Discomfort | 2 (2.5%) | 1 (0.6%) | 3 (1.2%) | 0 |
| Dyspepsia | 0 | 3 (1.9%) | 3 (1.2%) | 0 |
| Metabolism and Nutrition Disorders | | | | |
| Hypercholesterolemia | 1 (1.3%) | 2 (1.2%) | 3 (1.2%) | 0 |
| Nervous System Disorders | | | | |
| Dizziness | 4 (5.0%) | 3 (1.9%) | 7 (2.9%) | 0 |
| Headache | 1 (1.3%) | 4 (2.5%) | 5 (2.1%) | 0 |
| Psychiatric Disorders | | | | |
| Insomnia | 1 (1.3%) | 2 (1.2%) | 3 (1.2%) | 0 |

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Table 37

### 2.1.5.2.4. ART-Naive Adolescent Subjects

#### 2.1.5.2.4.1. Study GS-US-292-0106

Detailed AE results for the Phase 2/3 Study GS-US-292-0106 may be found in the CSR (GS-US-292-0106 Interim CSR, Section 11.2).

Adverse events that occurred in ≥ 5% of subjects in Study GS-US-292-0106 are summarized in Table 37. Adverse events by PT reported for at least 10% of subjects were nausea (22.9%, 11 subjects); upper respiratory tract infection (20.8%, 10 subjects); diarrhea (16.7%, 8 subjects); headache, respiratory tract infection, abdominal pain (each 14.6%, 7 subjects), vomiting (12.5%, 6 subjects), and dizziness and vitamin D deficiency (both 10.4%, 5 subjects).

**Table 37. E/C/F/TAF Study GS-US-292-0106: Adverse Events Occurring in ≥ 5% of Subjects (Safety Analysis Set)**

| Adverse Event by System Organ Class and Preferred Term[a,b] | E/C/F/TAF (N = 48) |
|---|---|
| Subjects Experiencing Any Adverse Event | 39 (81.3%) |
| Gastrointestinal disorders | 21 (43.8%) |
| Nausea | 11 (22.9%) |
| Diarrhoea | 8 (16.7%) |
| Abdominal pain | 7 (14.6%) |
| Vomiting | 6 (12.5%) |
| Abdominal pain upper | 3 (6.3%) |
| Infections and infestations | 19 (39.6%) |
| Upper respiratory tract infection | 10 (20.8%) |
| Respiratory tract infection | 7 (14.6%) |
| Body tinea | 4 (8.3%) |
| Bronchopneumonia | 4 (8.3%) |
| Urinary tract infection | 3 (6.3%) |
| Metabolism and nutrition disorders | 5 (10.4%) |
| Vitamin D deficiency | 5 (10.4%) |
| Nervous system disorders | 12 (25.0%) |
| Headache | 7 (14.6%) |
| Dizziness | 5 (10.4%) |
| Somnolence | 3 (6.3%) |
| Skin and subcutaneous tissue disorders | 3 (6.3%) |
| Rash papular | 3 (6.3%) |

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively. System organ class was presented alphabetically and PT was presented by descending order of the total frequencies.
Source: GS-US-292-0106 Interim CSR, Section 15.1, Table 16

### Adverse Events by Severity

Most AEs reported were Grade 1 or Grade 2 in severity (Table 24). Four subjects (8.3%) had a Grade 3 or Grade 4 AE. Grade 3 neuralgia was reported for 1 subject; Grade 3 bipolar disorder, conduct disorder, mania, and substance abuse were reported for 1 subject; Grade 3 chorioretinitis was reported for 1 subject; Grade 3 drug abuse and Grade 4 suicide attempt were reported for 1 subject.

### Adverse Events Considered Related to Study Drug

Adverse events related to study drug were reported for 18 subjects (37.5%) (Table 38). Study drug-related AEs that occurred in > 1 subject were either gastrointestinal, including nausea (10 subjects, 20.8%), abdominal pain (6 subjects, 12.5%), vomiting (5 subjects, 10.4%), and upper abdominal pain and diarrhea (both 3 subjects, 6.3%), or nervous system disorders, including somnolence (3 subjects, 6.3%), dizziness (4.2%, 2 subjects), and headache (4.2%, 2 subjects). With the exception of 1 event each of Grade 2 visual impairment, Grade 3 chorioretinitis, Grade 2 intermediate uveitis, (all reported for 1 subject), and Grade 2 headache (1 subject), all of the study drug-related AEs were Grade 1 in severity.

**Table 38. E/C/F/TAF Study GS-US-292-0106: Study Drug-Related Adverse Event (Safety Analysis Set)**

| Adverse Event by System Organ Class and Preferred Term[a,b] | E/C/F/TAF (N = 48) |
|---|---|
| Subjects Experiencing Any Adverse Event Related to Study Drug | 18 (37.5%) |
| Eye disorders | 1 (2.1%) |
| Intermediate uveitis | 1 (2.1%) |
| Visual impairment | 1 (2.1%) |
| Gastrointestinal disorders | 17 (35.4%) |
| Nausea | 10 (20.8%) |
| Abdominal pain | 6 (12.5%) |
| Vomiting | 5 (10.4%) |
| Abdominal pain upper | 3 (6.3%) |
| Diarrhoea | 3 (6.3%) |
| Dyspepsia | 1 (2.1%) |
| Flatulence | 1 (2.1%) |
| General disorders and administration site conditions | 1 (2.1%) |
| Fatigue | 1 (2.1%) |
| Infections and infestations | 1 (2.1%) |
| Chorioretinitis | 1 (2.1%) |
| Metabolism and nutrition disorders | 2 (4.2%) |
| Decreased appetite | 1 (2.1%) |
| Increased appetite | 1 (2.1%) |
| Nervous System Disorders | 7 (14.6%) |
| Somnolence | 3 (6.3%) |
| Dizziness | 2 (4.2%) |
| Headache | 2 (4.2%) |
| Lethargy | 1 (2.1%) |

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively. System organ class was presented alphabetically and PT was presented by descending order of the total frequencies.
Source: GS-US-292-0106 Interim CSR, Section 15.1, Table 19

### 2.1.5.3. RPV Studies

#### 2.1.5.3.1. ART-Naive Subjects

##### 2.1.5.3.1.1. Studies C209 and C215

This section provides a summary of AEs in the Phase 3 Week 96 pooled analysis for the overall dataset and the FTC/TDF subset, as well as in the individual Phase 3 trials, C209 (TMC278-C209-W96-CSR, Section 4.4.2) and C215 (TMC278-C215-W96-CSR, Section 4.4.2).

Adverse events reported in ≥ 5% of subjects in the FTC/TDF subset in either treatment group are presented in Table 39.

**Table 39. RPV Studies C209 and C215 (FTC/TDF Subset): Treatment-Emergent Adverse Events Reported in ≥ 5% of Subjects (by System Organ Class or Preferred Term) in the Rilpivirine or Control Group (Regardless of Severity and Drug Relatedness) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class and Preferred Term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 |
| **Infections and Infestations** | **231 (66.8)** | **230 (66.9)** | **147 (72.1)** | **135 (66.8)** | **378 (68.7)** | **365 (66.8)** |
| Nasopharyngitis | 41 (11.8) | 44 (12.8) | 40 (19.6) | 38 (18.8) | 81 (14.7) | 82 (15.0) |
| Upper Respiratory Tract Infection | 49 (14.2) | 46 (13.4) | 28 (13.7) | 19 (9.4) | 77 (14.0) | 65 (11.9) |
| Influenza | 35 (10.1) | 33 (9.6) | 14 (6.9) | 20 (9.9) | 49 (8.9) | 53 (9.7) |
| Bronchitis | 16 (4.6) | 15 (4.4) | 21 (10.3) | 3 (1.5) | 37 (6.7) | 18 (3.3) |
| Pharyngitis | 17 (4.9) | 16 (4.7) | 14 (6.9) | 7 (3.5) | 31 (5.6) | 23 (4.2) |
| Sinusitis | 16 (4.6) | 13 (3.8) | 12 (5.9) | 8 (4.0) | 28 (5.1) | 21 (3.8) |
| Syphilis | 17 (4.9) | 15 (4.4) | 11 (5.4) | 9 (4.5) | 28 (5.1) | 24 (4.4) |
| **Gastrointestinal Disorders** | **161 (46.5)** | **133 (38.7)** | **99 (48.5)** | **90 (44.6)** | **260 (47.3)** | **223 (40.8)** |
| Diarrhoea | 48 (13.9) | 59 (17.2) | 38 (18.6) | 32 (15.8) | 86 (15.6) | 91 (16.7) |
| Nausea | 43 (12.4) | 35 (10.2) | 28 (13.7) | 28 (13.9) | 71 (12.9) | 63 (11.5) |
| Vomiting | 15 (4.3) | 20 (5.8) | 11 (5.4) | 13 (6.4) | 26 (4.7) | 33 (6.0) |
| **Nervous System Disorders** | **99 (28.6)** | **156 (45.3)** | **81 (39.7)** | **109 (54.0)** | **180 (32.7)** | **265 (48.5)** |
| Headache | 48 (13.9) | 43 (12.5) | 38 (18.6) | 38 (18.8) | 86 (15.6) | 81 (14.8) |
| Dizziness | 27 (7.8) | 91 (26.5) | 30 (14.7) | 65 (32.2) | 57 (10.4) | 156 (28.6) |
| Somnolence | 13 (3.8) | 23 (6.7) | 4 (2.0) | 10 (5.0) | 17 (3.1) | 33 (6.0) |
| **Psychiatric Disorders** | **98 (28.3)** | **126 (36.6)** | **62 (30.4)** | **65 (32.2)** | **160 (29.1)** | **191 (35.0)** |
| Insomnia | 36 (10.4) | 37 (10.8) | 22 (10.8) | 12 (5.9) | 58 (10.5) | 49 (9.0) |
| Abnormal Dreams | 29 (8.4) | 41 (11.9) | 14 (6.9) | 21 (10.4) | 43 (7.8) | 62 (11.4) |
| Depression | 25 (7.2) | 23 (6.7) | 16 (7.8) | 8 (4.0) | 41 (7.5) | 31 (5.7) |
| Anxiety | 8 (2.3) | 27 (7.8) | 10 (4.9) | 10 (5.0) | 18 (3.3) | 37 (6.8) |
| **Skin and Subcutaneous Tissue Disorders** | **88 (25.4)** | **122 (35.5)** | **72 (35.3)** | **76 (37.6)** | **160 (29.1)** | **198 (36.3)** |
| Rash | 26 (7.5) | 43 (12.5) | 10 (4.9) | 30 (14.9) | 36 (6.5) | 73 (13.4) |
| **Musculoskeletal and Connective Tissue Disorders** | **75 (21.7)** | **79 (23.0)** | **49 (24.0)** | **54 (26.7)** | **124 (22.5)** | **133 (24.4)** |
| Back Pain | 18 (5.2) | 25 (7.3) | 10 (4.9) | 21 (10.4) | 28 (5.1) | 46 (8.4) |
| Arthralgia | 13 (3.8) | 19 (5.5) | 7 (3.4) | 13 (6.4) | 20 (3.6) | 32 (5.9) |

| System Organ Class and Preferred Term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 |
| **Investigations** | **60 (17.3)** | **68 (19.8)** | **48 (23.5)** | **37 (18.3)** | **108 (19.6)** | **105 (19.2)** |
| **Respiratory, Thoracic and Mediastinal Disorders** | **55 (15.9)** | **60 (17.4)** | **53 (26.0)** | **34 (16.8)** | **108 (19.6)** | **94 (17.2)** |
| Cough | 20 (5.8) | 18 (5.2) | 24 (11.8) | 10 (5.0) | 44 (8.0) | 28 (5.1) |
| **General Disorders and Administration Site Conditions** | **66 (19.1)** | **87 (25.3)** | **35 (17.2)** | **44 (21.8)** | **101 (18.4)** | **131 (24.0)** |
| Fatigue | 20 (5.8) | 31 (9.0) | 13 (6.4) | 21 (10.4) | 33 (6.0) | 52 (9.5) |
| **Injury, Poisoning and Procedural Complications** | **33 (9.5)** | **43 (12.5)** | **27 (13.2)** | **21 (10.4)** | **60 (10.9)** | **64 (11.7)** |
| **Metabolism and Nutrition Disorders** | **37 (10.7)** | **45 (13.1)** | **19 (9.3)** | **30 (14.9)** | **56 (10.2)** | **75 (13.7)** |
| **Renal and Urinary Disorders** | **32 (9.2)** | **22 (6.4)** | **22 (10.8)** | **16 (7.9)** | **54 (9.8)** | **38 (7.0)** |
| **Blood and Lymphatic System Disorders** | **31 (9.0)** | **22 (6.4)** | **21 (10.3)** | **19 (9.4)** | **52 (9.5)** | **41 (7.5)** |
| **Reproductive System and Breast Disorders** | **36 (10.4)** | **26 (7.6)** | **15 (7.4)** | **24 (11.9)** | **51 (9.3)** | **50 (9.2)** |
| **Vascular Disorders** | **24 (6.9)** | **27 (7.8)** | **21 (10.3)** | **15 (7.4)** | **45 (8.2)** | **42 (7.7)** |
| Hypertension | 18 (5.2) | 17 (4.9) | 15 (7.4) | 7 (3.5) | 33 (6.0) | 24 (4.4) |
| **Cardiac Disorders** | **21 (6.1)** | **27 (7.8)** | **14 (6.9)** | **12 (5.9)** | **35 (6.4)** | **39 (7.1)** |
| **Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)** | **18 (5.2)** | **17 (4.9)** | **16 (7.8)** | **11 (5.4)** | **34 (6.2)** | **28 (5.1)** |
| **Eye Disorders** | **20 (5.8)** | **21 (6.1)** | **13 (6.4)** | **21 (10.4)** | **33 (6.0)** | **42 (7.7)** |
| **Ear and Labyrinth Disorders** | **13 (3.8)** | **33 (9.6)** | **2 (1.0)** | **8 (4.0)** | **15 (2.7)** | **41 (7.5)** |

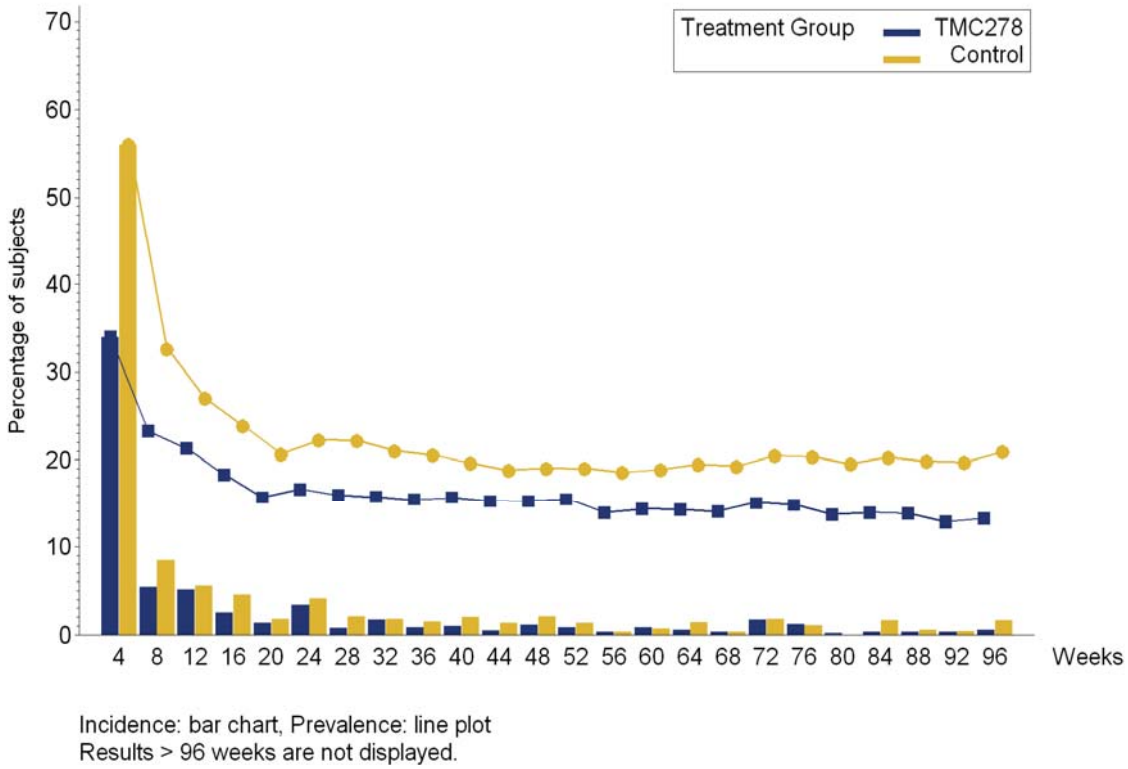
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.4, TMC278-C215-W96-Anal-Saf-AE/Display Ad Hoc and TMC278-C904-W96-Anal-Saf-AE/Display SAF.6

Similar to the overall population, by PT, the most commonly reported AEs in the RPV group were headache (15.6%), diarrhea (15.6%), nasopharyngitis (14.7%), upper respiratory tract infection (14.0%), nausea (12.9%), insomnia (10.5%), and dizziness (10.4%) in the FTC/TDF subset. All these events, except dizziness (10.4% vs 28.6%, respectively), were reported at a similar incidence in the RPV and control groups.

### Adverse Events, Causality and Severity

Figure 2 graphically presents the incidence and prevalence of treatment-related AEs over time for the overall Week 96 pooled analysis.

**Figure 2.** **RPV Studies C209 and C215: Incidence (Bars) and Prevalence (Lines) of Treatment-Emergent, Treatment-Related Adverse Events Over Time (Phase 3 Week 96 Pooled Analysis)**




Source: TMC278-C904-W96-Anal-Saf-AE/Display SAF.17.

Most treatment-related AEs were reported in the first 4 weeks of treatment for both RPV and control. The incidence and prevalence of these AEs were lower in the RPV than in the control group throughout the 96-week treatment period, however, the differences between treatment groups in incidence and prevalence were less pronounced after Week 4 and Week 8, respectively.

### Treatment-Related Adverse Events Reported in ≥ 1% of Subjects

The incidence of treatment-related AEs reported in ≥ 1% of subjects in either treatment group is presented in Table 40.

**Table 40. RPV Studies C209 and C215: Treatment-Related Adverse Events Reported in ≥ 1% of Subjects in the RPV or Control Group (Regardless of Severity) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Any treatment-related[a] AE** | **150 (43.4)** | **220 (64.0)** | **180 (52.9)** | **226 (66.9)** | **330 (48.1)** | **446 (65.4)** |
| **Gastrointestinal Disorders** | **58 (16.8)** | **46 (13.4)** | **78 (22.9)** | **77 (22.8)** | **136 (19.8)** | **123 (18.0)** |
| Nausea | 32 (9.2) | 24 (7.0) | 40 (11.8) | 55 (16.3) | 72 (10.5) | 79 (11.6) |
| Diarrhea | 14 (4.0) | 21 (6.1) | 15 (4.4) | 12 (3.6) | 29 (4.2) | 33 (4.8) |
| Vomiting | 7 (2.0) | 9 (2.6) | 7 (2.1) | 16 (4.7) | 14 (2.0) | 25 (3.7) |
| Flatulence | 6 (1.7) | 2 (0.6) | 3 (0.9) | 2 (0.6) | 9 (1.3) | 4 (0.6) |
| Abdominal pain upper | 1 (0.3) | 3 (0.9) | 6 (1.8) | 2 (0.6) | 7 (1.0) | 5 (0.7) |
| **Nervous System Disorders** | **54 (15.6)** | **117 (34.0)** | **68 (20.0)** | **135 (39.9)** | **122 (17.8)** | **252 (37.0)** |
| Dizziness | 22 (6.4) | 85 (24.7) | 33 (9.7) | 97 (28.7) | 55 (8.0) | 182 (26.7) |
| Headache | 22 (6.4) | 14 (4.1) | 21 (6.2) | 25 (7.4) | 43 (6.3) | 39 (5.7) |
| Somnolence | 12 (3.5) | 21 (6.1) | 14 (4.1) | 28 (8.3) | 26 (3.8) | 49 (7.2) |
| Disturbance in attention | 2 (0.6) | 10 (2.9) | 3 (0.9) | 7 (2.1) | 5 (0.7) | 17 (2.5) |
| **Psychiatric Disorders** | **53 (15.3)** | **94 (27.3)** | **54 (15.9)** | **72 (21.3)** | **107 (15.6)** | **166 (24.3)** |
| Abnormal dreams | 27 (7.8) | 39 (11.3) | 18 (5.3) | 26 (7.7) | 45 (6.6) | 65 (9.5) |
| Insomnia | 14 (4.0) | 24 (7.0) | 21 (6.2) | 17 (5.0) | 35 (5.1) | 41 (6.0) |
| Depression | 8 (2.3) | 11 (3.2) | 7 (2.1) | 7 (2.1) | 15 (2.2) | 18 (2.6) |
| Nightmare | 7 (2.0) | 12 (3.5) | 8 (2.4) | 15 (4.4) | 15 (2.2) | 27 (4.0) |
| Sleep disorder | 2 (0.6) | 13 (3.8) | 7 (2.1) | 9 (2.7) | 9 (1.3) | 22 (3.2) |
| Anxiety | 2 (0.6) | 9 (2.6) | 2 (0.6) | 6 (1.8) | 4 (0.6) | 15 (2.2) |
| **Skin and Subcutaneous Tissue Disorders** | **21 (6.1)** | **61 (17.7)** | **28 (8.2)** | **50 (14.8)** | **49 (7.1)** | **111 (16.3)** |
| Rash | 11 (3.2) | 29 (8.4) | 6 (1.8) | 31 (9.2) | 17 (2.5) | 60 (8.8) |
| Pruritus | 1 (0.3) | 10 (2.9) | 9 (2.6) | 6 (1.8) | 10 (1.5) | 16 (2.3) |
| Rash maculo-papular | 0 | 4 (1.2) | 0 | 6 (1.8) | 0 | 10 (1.5) |
| **General Disorders and Administration Site Conditions** | **24 (6.9)** | **43 (12.5)** | **23 (6.8)** | **30 (8.9)** | **47 (6.9)** | **73 (10.7)** |
| Fatigue | 11 (3.2) | 15 (4.4) | 10 (2.9) | 14 (4.1) | 21 (3.1) | 29 (4.3) |
| Irritability | 6 (1.7) | 6 (1.7) | 2 (0.6) | 2 (0.6) | 8 (1.2) | 8 (1.2) |
| Asthenia | 4 (1.2) | 7 (2.0) | 3 (0.9) | 7 (2.1) | 7 (1.0) | 14 (2.1) |
| Feeling abnormal | 1 (0.3) | 5 (1.5) | 0 | 2 (0.6) | 1 (0.1) | 7 (1.0) |

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Investigations** | **20 (5.8)** | **25 (7.3)** | **27 (7.9)** | **31 (9.2)** | **47 (6.9)** | **56 (8.2)** |
| ALT increased | 1 (0.3) | 6 (1.7) | 7 (2.1) | 3 (0.9) | 8 (1.2) | 9 (1.3) |
| AST increased | 2 (0.6) | 5 (1.5) | 6 (1.8) | 2 (0.6) | 8 (1.2) | 7 (1.0) |
| Blood cortisol decreased | 5 (1.4) | 2 (0.6) | 3 (0.9) | 1 (0.3) | 8 (1.2) | 3 (0.4) |
| ECG QT prolonged | 0 | 1 (0.3) | 2 (0.6) | 10 (3.0) | 2 (0.3) | 11 (1.6) |
| Blood triglycerides increased | 0 | 5 (1.5) | 0 | 4 (1.2) | 0 | 9 (1.3) |
| **Metabolism and Nutrition Disorders** | **13 (3.8)** | **24 (7.0)** | **7 (2.1)** | **27 (8.0)** | **20 (2.9)** | **51 (7.5)** |
| Hypercholesterolemia | 3 (0.9) | 2 (0.6) | 1 (0.3) | 8 (2.4) | 4 (0.6) | 10 (1.5) |
| Anorexia | 1 (0.3) | 4 (1.2) | 2 (0.6) | 3 (0.9) | 3 (0.4) | 7 (1.0) |
| Decreased appetite | 1 (0.3) | 4 (1.2) | 1 (0.3) | 4 (1.2) | 2 (0.3) | 8 (1.2) |
| Hyperlipidemia | 1 (0.3) | 7 (2.0) | 1 (0.3) | 3 (0.9) | 2 (0.3) | 10 (1.5) |
| Hypertriglyceridemia | 2 (0.6) | 3 (0.9) | 0 | 6 (1.8) | 2 (0.3) | 9 (1.3) |
| **Cardiac Disorders** | **5 (1.4)** | **9 (2.6)** | **8 (2.4)** | **11 (3.3)** | **13 (1.9)** | **20 (2.9)** |
| Palpitations | 1 (0.3) | 5 (1.5) | 1 (0.3) | 2 (0.6) | 2 (0.3) | 7 (1.0) |
| **Musculoskeletal and Connective Tissue Disorders** | **2 (0.6)** | **6 (1.7)** | **5 (1.5)** | **8 (2.4)** | **7 (1.0)** | **14 (2.1)** |
| Myalgia | 1 (0.3) | 3 (0.9) | 2 (0.6) | 4 (1.2) | 3 (0.4) | 7 (1.0) |
| **Vascular Disorders** | **2 (0.6)** | **7 (2.0)** | **5 (1.5)** | **7 (2.1)** | **7 (1.0)** | **14 (2.1)** |
| **Blood and Lymphatic System Disorders** | **2 (0.6)** | **4 (1.2)** | **4 (1.2)** | **4 (1.2)** | **6 (0.9)** | **8 (1.2)** |
| **Reproductive System and Breast Disorders** | **5 (1.4)** | **6 (1.7)** | **1 (0.3)** | **1 (0.3)** | **6 (0.9)** | **7 (1.0)** |
| **Ear and Labyrinth Disorders** | **2 (0.6)** | **16 (4.7)** | **1 (0.3)** | **4 (1.2)** | **3 (0.4)** | **20 (2.9)** |
| Vertigo | 2 (0.6) | 13 (3.8) | 0 | 3 (0.9) | 2 (0.3) | 16 (2.3) |
| **Infections and Infestations** | **2 (0.6)** | **5 (1.5)** | **0** | **4 (1.2)** | **2 (0.3)** | **9 (1.3)** |

Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.9, TMC278-C215-W96-Anal-Saf-AE/Display SAF.9 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.13.

The incidence of treatment-related AEs was lower in the RPV group (48.1%) than in the control group (65.4%).

By PT, the most frequently reported treatment-related AEs in the RPV group were nausea (10.5% in the RPV group vs 11.6% in the control group), dizziness (8.0% vs 26.7%, respectively), abnormal dreams (6.6% vs 9.5%, respectively), headache (6.3% vs 5.7%, respectively), and insomnia (5.1% vs 6.0%, respectively).

The greatest differences in incidence between treatment groups were seen for the PTs dizziness, somnolence, rash, disturbance in attention, and vertigo which were each reported at a lower incidence in the RPV group (8.0%, 3.8%, 2.5%, 0.7% [5 subjects], and 0.3% [2 subjects], respectively) than in the control group (26.7%, 7.2%, 8.8%, 2.5%, and 2.3%, respectively).

Statistical testing comparing RPV with control in the incidence of treatment-related AEs reported in > 10% of subjects (by PT, using the Fisher's Exact test), revealed highly statistically significant differences in favor of RPV for dizziness ($p < 0.0001$) and statistically significant differences in favor of RPV for abnormal dreams/nightmare ($p = 0.0039$). No statistically significant differences were found in favor of control for any of the AEs tested (TMC278-C904-W96-Anal-Saf-AE/Display SAF.6).

There were no substantial differences in the RPV group in the incidence of treatment-related AEs observed in trial C209 compared with trial C215, except in gastrointestinal disorders (16.8% vs 22.9%, respectively), driven by nausea (9.2% vs 11.8%, respectively).

Treatment-related AEs, regardless of severity, are summarized for the FTC/TDF subset in TMC278-C904-W96-Anal-ADD/Display Ad Hoc.

**Treatment-Related Adverse Events of at Least Grade 2 in Severity, and Reported in ≥ 1% of Subjects**

Table 41 summarizes treatment-related AEs with a severity grade of at least 2 reported in ≥ 1% of subjects in either treatment group.

**Table 41. RPV Studies C209 and C215: Treatment-Related Adverse Events of at Least Grade 2 in Severity, and Reported in ≥ 1% of Subjects in the RPV or Control Group (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Any treatment-related[a] AE of at least Grade 2** | **61 (17.6)** | **115 (33.4)** | **55 (16.2)** | **111 (32.8)** | **116 (16.9)** | **226 (33.1)** |
| **Psychiatric Disorders** | **18 (5.2)** | **38 (11.0)** | **23 (6.8)** | **27 (8.0)** | **41 (6.0)** | **65 (9.5)** |
| Insomnia | 5 (1.4) | 10 (2.9) | 8 (2.4) | 7 (2.1) | 13 (1.9) | 17 (2.5) |
| Depression | 6 (1.7) | 6 (1.7) | 5 (1.5) | 6 (1.8) | 11 (1.6) | 12 (1.8) |
| Abnormal dreams | 4 (1.2) | 12 (3.5) | 4 (1.2) | 4 (1.2) | 8 (1.2) | 16 (2.3) |
| Anxiety | 2 (0.6) | 6 (1.7) | 1 (0.3) | 2 (0.6) | 3 (0.4) | 8 (1.2) |
| Nightmare | 2 (0.6) | 7 (2.0) | 0 | 3 (0.9) | 2 (0.3) | 10 (1.5) |
| **Nervous System Disorders** | **16 (4.6)** | **35 (10.2)** | **7 (2.1)** | **34 (10.1)** | **23 (3.4)** | **69 (10.1)** |
| Headache | 6 (1.7) | 6 (1.7) | 5 (1.5) | 9 (2.7) | 11 (1.6) | 15 (2.2) |
| Dizziness | 4 (1.2) | 23 (6.7) | 0 | 21 (6.2) | 4 (0.6) | 44 (6.5) |
| Somnolence | 2 (0.6) | 5 (1.5) | 2 (0.6) | 4 (1.2) | 4 (0.6) | 9 (1.3) |
| **Gastrointestinal Disorders** | **9 (2.6)** | **15 (4.4)** | **12 (3.5)** | **18 (5.3)** | **21 (3.1)** | **33 (4.8)** |
| Diarrhea | 4 (1.2) | 5 (1.5) | 3 (0.9) | 4 (1.2) | 7 (1.0) | 9 (1.3) |
| Nausea | 4 (1.2) | 8 (2.3) | 1 (0.3) | 9 (2.7) | 5 (0.7) | 17 (2.5) |
| Vomiting | 0 | 3 (0.9) | 2 (0.6) | 7 (2.1) | 2 (0.3) | 10 (1.5) |
| **Investigations** | **8 (2.3)** | **14 (4.1)** | **11 (3.2)** | **15 (4.4)** | **19 (2.8)** | **29 (4.3)** |
| AST increased | 2 (0.6) | 2 (0.6) | 5 (1.5) | 2 (0.6) | 7 (1.0) | 4 (0.6) |
| Blood triglycerides increased | 0 | 5 (1.5) | 0 | 2 (0.6) | 0 | 7 (1.0) |
| **General Disorders and Administration Site Conditions** | **5 (1.4)** | **21 (6.1)** | **8 (2.4)** | **5 (1.5)** | **13 (1.9)** | **26 (3.8)** |
| **Metabolism and Nutrition Disorders** | **8 (2.3)** | **8 (2.3)** | **4 (1.2)** | **12 (3.6)** | **12 (1.7)** | **20 (2.9)** |
| Hyperlipidemia | 1 (0.3) | 4 (1.2) | 1 (0.3) | 3 (0.9) | 2 (0.3) | 7 (1.0) |
| **Skin and Subcutaneous Tissue Disorders** | **7 (2.0)** | **28 (8.1)** | **4 (1.2)** | **32 (9.5)** | **11 (1.6)** | **60 (8.8)** |
| Rash | 3 (0.9) | 15 (4.4) | 1 (0.3) | 21 (6.2) | 4 (0.6) | 36 (5.3) |
| Rash maculo-papular | 0 | 3 (0.9) | 0 | 6 (1.8) | 0 | 9 (1.3) |
| **Ear and Labyrinth Disorders** | **0** | **4 (1.2)** | **1 (0.3)** | **4 (1.2)** | **1 (0.1)** | **8 (1.2)** |

[a] Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.1 and Display SAF.13; TMC278-C215-W96-Anal-Saf-AE/Display SAF.1 and Display SAF.13, and TMC278-C904-W96-Anal-Saf-AE/Display SAF.1 and Display SAF.22.

The incidence of treatment-related AEs with a severity grade of at least 2 was lower in the RPV group than in the control group (16.9% vs 33.1%, respectively).

In the RPV group, no individual treatment-related AE with a severity grade of at least 2 was reported in ≥ 2.0% of subjects. The most common treatment-related AEs in the RPV group with a severity grade of at least 2 were insomnia (1.9% in the RPV group vs 2.5% in the control group), depression (1.6% vs 1.8%, respectively), headache (1.6% vs 2.2%, respectively) and abnormal dreams (1.2% [8 subjects] vs 2.3%, respectively).

### Grade 3 or 4 Treatment-Emergent Adverse Events Reported in ≥ 0.5% of Subjects

Grade 3 and 4 AEs reported in ≥ 0.5% of subjects in the RPV or control group (irrespective of causality) are presented in Table 42.

**Table 42. RPV Studies C209 and C215: Grade 3 or 4 Treatment-Emergent Adverse Events Reported in ≥ 0.5% of Subjects in the RPV or Control Group (Regardless of Drug Relatedness) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Any AE of at least Grade 3** | **53 (15.3)** | **73 (21.2)** | **67 (19.7)** | **66 (19.5)** | **120 (17.5)** | **139 (20.4)** |
| **Investigations** | **13 (3.8)** | **23 (6.7)** | **22 (6.5)** | **29 (8.6)** | **35 (5.1)** | **52 (7.6)** |
| Blood amylase increased | 7 (2.0) | 4 (1.2) | 2 (0.6) | 4 (1.2) | 9 (1.3) | 8 (1.2) |
| AST increased | 2 (0.6) | 3 (0.9) | 5 (1.5) | 5 (1.5) | 7 (1.0) | 8 (1.2) |
| Neutrophil count decreased | 0 | 2 (0.6) | 7 (2.1) | 10 (3.0) | 7 (1.0) | 12 (1.8) |
| ALT increased | 1 (0.3) | 5 (1.5) | 4 (1.2) | 7 (2.1) | 5 (0.7) | 12 (1.8) |
| Lipase increased | 2 (0.6) | 3 (0.9) | 2 (0.6) | 2 (0.6) | 4 (0.6) | 5 (0.7) |
| Blood triglycerides increased | 0 | 3 (0.9) | 0 | 2 (0.6) | 0 | 5 (0.7) |
| **Infections and Infestations** | **10 (2.9)** | **11 (3.2)** | **11 (3.2)** | **10 (3.0)** | **21 (3.1)** | **21 (3.1)** |
| **Blood and Lymphatic System Disorders** | **7 (2.0)** | **4 (1.2)** | **11 (3.2)** | **6 (1.8)** | **18 (2.6)** | **10 (1.5)** |
| Neutropenia | 3 (0.9) | 3 (0.9) | 7 (2.1) | 4 (1.2) | 10 (1.5) | 7 (1.0) |
| Leukopenia | 2 (0.6) | 0 | 2 (0.6) | 0 | 4 (0.6) | 0 |
| **Psychiatric Disorders** | **9 (2.6)** | **13 (3.8)** | **4 (1.2)** | **4 (1.2)** | **13 (1.9)** | **17 (2.5)** |
| Depression | 3 (0.9) | 4 (1.2) | 2 (0.6) | 1 (0.3) | 5 (0.7) | 5 (0.7) |
| Suicidal ideation | 3 (0.9) | 2 (0.6) | 1 (0.3) | 0 | 4 (0.6) | 2 (0.3) |
| **Gastrointestinal Disorders** | **4 (1.2)** | **5 (1.5)** | **5 (1.5)** | **4 (1.2)** | **9 (1.3)** | **9 (1.3)** |
| Nausea | 0 | 1 (0.3) | 0 | 3 (0.9) | 0 | 4 (0.6) |
| **Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)** | **7 (2.0)** | **4 (1.2)** | **1 (0.3)** | **0** | **8 (1.2)** | **4 (0.6)** |
| **Hepatobiliary Disorders** | **2 (0.6)** | **4 (1.2)** | **5 (1.5)** | **3 (0.9)** | **7 (1.0)** | **7 (1.0)** |

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Injury, Poisoning, and Procedural Complications** | **4 (1.2)** | **4 (1.2)** | **3 (0.9)** | **3 (0.9)** | **7 (1.0)** | **7 (1.0)** |
| **Nervous System Disorders** | **3 (0.9)** | **7 (2.0)** | **3 (0.9)** | **5 (1.5)** | **6 (0.9)** | **12 (1.8)** |
| **Musculoskeletal and Connective Tissue Disorders** | **2 (0.6)** | **2 (0.6)** | **3 (0.9)** | **1 (0.3)** | **5 (0.7)** | **3 (0.4)** |
| **Skin and Subcutaneous Tissue Disorders** | **2 (0.6)** | **2 (0.6)** | **3 (0.9)** | **5 (1.5)** | **5 (0.7)** | **7 (1.0)** |
| Rash | 1 (0.3) | 1 (0.3) | 0 | 3 (0.9) | 1 (0.1) | 4 (0.6) |
| **Renal and Urinary Disorders** | **3 (0.9)** | **1 (0.3)** | **1 (0.3)** | **3 (0.9)** | **4 (0.6)** | **4 (0.6)** |
| **Vascular Disorders** | **1 (0.3)** | **0** | **3 (0.9)** | **2 (0.6)** | **4 (0.6)** | **2 (0.3)** |
| **Respiratory, Thoracic, and Mediastinal Disorders** | **1 (0.3)** | **6 (1.7)** | **2 (0.6)** | **2 (0.6)** | **3 (0.4)** | **8 (1.2)** |
| **General Disorders and Administration Site Conditions** | **0** | **4 (1.2)** | **2 (0.6)** | **1 (0.3)** | **2 (0.3)** | **5 (0.7)** |
| **Metabolism and Nutrition Disorders** | **0** | **7 (2.0)** | **2 (0.6)** | **7 (2.1)** | **2 (0.3)** | **14 (2.1)** |
| Hyperlipidemia | 0 | 3 (0.9) | 0 | 2 (0.6) | 0 | 5 (0.7) |

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.12, TMC278-C215-W96-Anal-Saf-AE/Display SAF.12 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.19.

Most AEs were Grade 1 or 2 in severity. Overall, the incidence of Grade 3 or 4 AEs was 17.5% in the RPV group and 20.4% in the control group. For details of Grade 3 or 4 AEs related to laboratory abnormalities, see Section 3.4.3.

By PT, no Grade 3 or 4 AEs occurred in > 1.5% of RPV-treated subjects. The most commonly reported Grade 3 or 4 AEs in the RPV group were neutropenia (1.5% in the RPV group vs 1.0% [7 subjects] in the control group), increased blood amylase (1.3% [9 subjects] vs 1.2% [8 subjects], respectively), increased AST (1.0% [7 subjects] vs 1.2% [8 subjects], respectively), and decreased neutrophil count (1.0% [7 subjects] vs 1.8%, respectively).

Grade 3 or 4 renal and urinary disorders were reported at low incidence in both treatment groups (0.6% [4 subjects]). None of the AEs were considered treatment-related.

### Treatment-Related AEs with a Severity Grade of at Least 2 Reported in ≥ 1% of Subjects in Either Treatment Group in the FTC/TDF Subset

For the FTC/TDF subset, in the RPV group, no individual treatment-related AE with a severity grade of at least 2 was reported in ≥ 5.0% of subjects. The most common treatment-related AEs in the RPV group with a severity grade of at least 2 were insomnia (2.0% vs 2.4% in the control group), headache (1.6% vs 2.2% in the control group), abnormal dreams (1.3% vs 2.7% in the control group), and depression (1.6% vs 1.8% in the control group).

#### 2.1.5.3.2. ART-Naive Adolescent Subjects

##### 2.1.5.3.2.1. Study C213

Detailed AE results for the Phase 2 Study C213 may be found in the CSR (TMC278-C213-W48-CSR, Section 8.2).

Adverse events reported in at least 5% of subjects are presented in Table 40.

The most frequently reported AEs were influenza, in 15 (41.7%) subjects, upper respiratory tract infection and cough, in 8 (22.2%) subjects each, and decreased blood cortisol, depression and headache, in 7 (19.4%) subjects each.

**Table 43 RPV Study C213: Incidence (%) of Adverse Events in at Least 5% of the Subjects (Intent-to-Treat)**

| n (%) | RPV 25 mg qd |
|---|---|
| Analysis set: intent-to-treat | 36 |
| Any AE | 35 (97.2%) |
| Infections and infestations | 29 (80.6%) |
| Influenza | 15 (41.7%) |
| Upper respiratory tract infection | 8 (22.2%) |
| Bronchitis | 4 (11.1%) |
| Sinusitis | 3 (8.3%) |
| Urinary tract infection | 3 (8.3%) |
| Abscess limb | 2 (5.6%) |
| Hepatitis B | 2 (5.6%) |
| Malaria | 2 (5.6%) |
| Nasopharyngitis | 2 (5.6%) |
| Tonsillitis | 2 (5.6%) |
| Gastrointestinal disorders | 15 (41.7%) |
| Nausea | 4 (11.1%) |
| Diarrhoea | 3 (8.3%) |
| Abdominal pain | 2 (5.6%) |
| Dental caries | 2 (5.6%) |
| Toothache | 2 (5.6%) |
| Vomiting | 2 (5.6%) |
| Investigations | 14 (38.9%) |
| Blood cortisol decreased | 7 (19.4%) |

| n (%) | RPV 25 mg qd |
|---|---|
| Weight decreased | 4 (11.1%) |
| Blood alkaline phosphatase increased | 3 (8.3%) |
| Protein total increased | 2 (5.6%) |
| Nervous system disorders | 13 (36.1%) |
| Headache | 7 (19.4%) |
| Somnolence | 5 (13.9%) |
| Dizziness | 3 (8.3%) |
| Respiratory, thoracic and mediastinal disorders | 10 (27.8%) |
| Cough | 8 (22.2%) |
| Productive cough | 2 (5.6%) |
| Psychiatric disorders | 8 (22.2%) |
| Depression | 7 (19.4%) |
| Blood and lymphatic system disorders | 6 (16.7%) |
| Anaemia | 4 (11.1%) |
| Skin and subcutaneous tissue disorders | 5 (13.9%) |
| Rash | 2 (5.6%) |
| Eye disorders | 4 (11.1%) |
| Conjunctivitis | 2 (5.6%) |
| General disorders and administration site conditions | 3 (8.3%) |
| Pyrexia | 2 (5.6%) |
| Renal and urinary disorders | 3 (8.3%) |
| Haematuria | 2 (5.6%) |
| Reproductive system and breast disorders | 3 (8.3%) |
| Vaginal discharge | 2 (5.6%) |
| Surgical and medical procedures | 2 (5.6%) |
| Tooth extraction | 2 (5.6%) |

Source: TMC278-C213-W48-CSR/Table 32

### Adverse Events by Severity

Adverse events with a severity of grade 3-4 were reported in 7 (19.4%) subjects. The most frequently reported grade 3-4 AEs (>1 subject) were malaria (2 subjects) and depression (2 subjects). There were no treatment-related grade 3-4 AEs reported.

### Adverse Events Considered Related to Study Drug

Treatment-related AEs were defined as AEs that were reported to be possibly, probably or very likely related to study treatment in the opinion of the investigator.

The incidence of treatment-related AEs is presented in Table 44. For a total of 13 (36.1%) subjects, treatment-related AEs were reported; the most frequently reported events were somnolence in 5 (13.9%) subjects and blood cortisol decreased in 3 (8.3%) subjects.

**Table 44 RPV Study C213: Incidence (%) of Adverse Events at Least Possibly Related to RPV (Intent-to-Treat)**

| n (%) | RPV 25 mg qd |
|---|---|
| Analysis set: intent-to-treat | 36 |
| Any AE at least possibly related to RPV | 13 (36.1%) |
| Nervous system disorders | 7 (19.4%) |
| Somnolence | 5 (13.9%) |
| Dizziness | 1 (2.8%) |
| Headache | 1 (2.8%) |
| Gastrointestinal disorders | 3 (8.3%) |
| Nausea | 2 (5.6%) |
| Abdominal pain upper | 1 (2.8%) |
| Investigations | 3 (8.3%) |
| Blood cortisol decreased | 3 (8.3%) |
| Blood alkaline phosphatase increased | 2 (5.6%) |
| Eye disorders | 1 (2.8%) |
| Vision blurred | 1 (2.8%) |
| General disorders and administration site conditions | 1 (2.8%) |
| Pyrexia | 1 (2.8%) |
| Immune system disorders | 1 (2.8%) |
| Drug hypersensitivity | 1 (2.8%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (2.8%) |
| Skin papilloma | 1 (2.8%) |
| Skin and subcutaneous tissue disorders | 1 (2.8%) |
| Rash | 1 (2.8%) |

Source: TMC278-C213-W48-CSR/Table 33

### 2.1.5.4. Complera/Eviplera Studies

#### 2.1.5.4.1. Virologically Suppressed Subjects

##### 2.1.5.4.1.1. Study GS-US-264-0111

Detailed AE results for the Phase 2b Study GS-US-264-0111 may be found in the CSR (GS-US-264-0111 CSR, Section 11.2).

Adverse events that were reported in at least 2 subjects (4.1%) in the safety analysis set for Study GS-US-264-0111 are presented in Table 45. Diarrhea was the most frequently occurring treatment-emergent AE (8 subjects [16.3%]), followed by upper respiratory tract infection (7 subjects [14.3%]) and insomnia (6 subjects [12.2%]).

**Table 45. Complera/Eviplera Study GS-US-264-0111: Treatment-Emergent Adverse Events Reported in at Least 2 Subjects (Safety Analysis Set)**

| | FTC/RPV/TDF (N = 49) | |
|---|---|---|
| **Adverse Events[a] by System Organ Class and Preferred Term** | **n** | **%** |
| Any Treatment-Emergent AE | 43 | 87.8% |
| Endocrine Disorders | 2 | 4.1% |
| Hypogonadism | 2 | 4.1% |
| Gastrointestinal Disorders | 20 | 40.8% |
| Diarrhoea | 8 | 16.3% |
| Abdominal Pain | 4 | 8.2% |
| Nausea | 3 | 6.1% |
| Flatulence | 2 | 4.1% |
| Rectal haemorrhage | 2 | 4.1% |
| Vomiting | 2 | 4.1% |
| General Disorders and Administration Site Conditions | 9 | 18.4% |
| Fatigue | 4 | 8.2% |
| Infections and Infestations | 22 | 44.9% |
| Upper respiratory tract infection | 7 | 14.3% |
| Sinusitis | 5 | 10.2% |
| Pharyngitis | 4 | 8.2% |
| Syphilis | 3 | 6.1% |
| Urethritis | 3 | 6.1% |
| Bronchitis | 2 | 4.1% |
| Influenza | 2 | 4.1% |
| Investigations | 5 | 10.2% |
| Anal pap smear abnormal | 2 | 4.1% |
| Metabolism and Nutrition Disorders | 4 | 8.2% |

| Adverse Events[a] by System Organ Class and Preferred Term | FTC/RPV/TDF (N = 49) | |
|---|---|---|
| | n | % |
| Vitamin D Deficiency | 2 | 4.1% |
| Musculoskeletal and Connective Tissue Disorders | 11 | 22.4% |
| Back pain | 4 | 8.2% |
| Psychiatric Disorders | 14 | 28.6% |
| Insomnia | 6 | 12.2% |
| Anxiety | 3 | 6.1% |
| Depression | 3 | 6.1% |
| Abnormal Dreams | 2 | 4.1% |
| Respiratory, Thoracic, and Mediastinal Disorders | 8 | 16.3% |
| Oropharyngeal Pain | 2 | 4.1% |
| Rhinitis Allergic | 2 | 4.1% |
| Skin and Subcutaneous Tissue Disorders | 8 | 16.3% |
| Dermatitis | 2 | 4.1% |
| Rash | 2 | 4.1% |

[a] Adverse events were mapped according to MedDRA version 15.
Source: GS-US-264-0111 CSR, Section 15.1, Table 5.1.2

### Adverse Events by Severity

Most AEs were Grade 1 or 2 in severity during Study GS-US-264-0111. Grade 2 or 3 AEs were reported in 21 subjects during the study (42.9%). No subject experienced a Grade 4 AE. There were 4 Grade 3 events reported in 3 subjects during the study: bradycardia and dyspnea in 1 subject (both SAEs; see Section 2.1.7.4.1.1), hematuria in 1 subject, and nephrolithiasis in 1 subject. The events of bradycardia and dyspnea were SAEs and are described in Section 2.1.7.4.1.1. The events of hematuria and nephrolithiasis were nonserious AEs and both resolved during the study. None of the Grade 3 AEs were considered by the investigator to be related to study drug.

### Adverse Events Considered Related to Study Drug

Twelve subjects (24.5%) experienced AEs that were considered by the investigator to be related to study drug during Study GS-US-264-0111. The highest incidence of treatment-related AEs was in the SOC of gastrointestinal disorders (7 subjects [14.3%]). Three subjects experienced Grade 2 treatment-related AEs (gastritis, fatigue, and increased bilirubin); all other treatment-related AEs were Grade 1 in severity. Grade 1 treatment-related AEs of flatulence, nausea, and insomnia occurred in 2 subjects each; all other Grade 1 treatment-related AEs occurred in 1 subject each.

#### 2.1.5.4.1.2. Study GS-US-264-0106

Detailed AE results for the Phase 3 Study GS-US-264-0106 may be found in the CSR (GS-US-264-0106 Week 48 CSR, Section 11.2).

Treatment-emergent AEs reported in at least 2% of subjects in the safety analysis set for Study GS-US-264-0106 are presented in Table 46. The most frequently (≥ 5% of subjects) occurring treatment-emergent AEs in subjects in the FTC/RPV/TDF group, receiving up to 48 weeks of treatment, included diarrhea (10.1%), nasopharyngitis (8.8%), headache (8.8%), insomnia (6.3%), fatigue (6.9%), cough (6.0%), and arthralgia (5.0%). The most frequently occurring treatment-emergent AEs in subjects in the SBR group were diarrhea (5.0%) and nasopharyngitis (5.0%). After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24, the most frequently occurring treatment-emergent AEs in the Delayed Switch group (receiving up to 24 weeks of FTC/RPV/TDF) included nausea (6.6%), upper respiratory tract infection (8.6%), nasopharyngitis (5.3%), and insomnia (5.3%).

**Table 46. Complera/Eviplera Study GS-US-264-0106: Treatment-Emergent Adverse Events Reported in at Least 2% of Subjects in Any Treatment Group (Safety Analysis Set)**

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| Subjects With Any Treatment-Emergent Adverse Event | 253 (79.8%) | 91 (57.2%) | 109 (71.7%) | 362 (77.2%) |
| Subjects With Any Treatment-Emergent Adverse Event By System Organ Class and Preferred Term | | | | |
| GASTROINTESTINAL DISORDERS | 86 (27.1%) | 26 (16.4%) | 43 (28.3%) | 129 (27.5%) |
| DIARRHOEA | 32 (10.1%) | 8 (5.0%) | 6 (3.9%) | 38 (8.1%) |
| NAUSEA | 12 (3.8%) | 5 (3.1%) | 10 (6.6%) | 22 (4.7%) |
| ABDOMINAL PAIN | 8 (2.5%) | 2 (1.3%) | 6 (3.9%) | 14 (3.0%) |
| CONSTIPATION | 7 (2.2%) | 3 (1.9%) | 5 (3.3%) | 12 (2.6%) |
| HAEMORRHOIDS | 5 (1.6%) | 1 (0.6%) | 3 (2.0%) | 8 (1.7%) |
| DYSPEPSIA | 2 (0.6%) | 2 (1.3%) | 5 (3.3%) | 7 (1.5%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 52 (16.4%) | 15 (9.4%) | 10 (6.6%) | 62 (13.2%) |
| FATIGUE | 22 (6.9%) | 5 (3.1%) | 3 (2.0%) | 25 (5.3%) |
| PYREXIA | 11 (3.5%) | 5 (3.1%) | 3 (2.0%) | 14 (3.0%) |
| CHEST PAIN | 4 (1.3%) | 2 (1.3%) | 4 (2.6%) | 8 (1.7%) |
| HEPATOBILIARY DISORDERS | 7 (2.2%) | 0 | 3 (2.0%) | 10 (2.1%) |
| CYTOLYTIC HEPATITIS | 1 (0.3%) | 0 | 3 (2.0%) | 4 (0.9%) |
| INFECTIONS AND INFESTATIONS | 125 (39.4%) | 47 (29.6%) | 49 (32.2%) | 174 (37.1%) |
| NASOPHARYNGITIS | 28 (8.8%) | 8 (5.0%) | 8 (5.3%) | 36 (7.7%) |
| UPPER RESPIRATORY TRACT INFECTION | 11 (3.5%) | 5 (3.1%) | 13 (8.6%) | 24 (5.1%) |
| BRONCHITIS | 13 (4.1%) | 4 (2.5%) | 5 (3.3%) | 18 (3.8%) |
| SINUSITIS | 10 (3.2%) | 4 (2.5%) | 1 (0.7%) | 11 (2.3%) |
| GASTROENTERITIS | 4 (1.3%) | 1 (0.6%) | 5 (3.3%) | 9 (1.9%) |

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| ORAL HERPES | 8 (2.5%) | 1 (0.6%) | 1 (0.7%) | 9 (1.9%) |
| HERPES SIMPLEX | 7 (2.2%) | 1 (0.6%) | 1 (0.7%) | 8 (1.7%) |
| SYPHILIS | 5 (1.6%) | 2 (1.3%) | 3 (2.0%) | 8 (1.7%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 29 (9.1%) | 10 (6.3%) | 11 (7.2%) | 40 (8.5%) |
| PROCEDURAL PAIN | 2 (0.6%) | 1 (0.6%) | 3 (2.0%) | 5 (1.1%) |
| INVESTIGATIONS | 34 (10.7%) | 5 (3.1%) | 11 (7.2%) | 45 (9.6%) |
| ALANINE AMINOTRANSFERASE INCREASED | 4 (1.3%) | 1 (0.6%) | 4 (2.6%) | 8 (1.7%) |
| METABOLISM AND NUTRITION DISORDERS | 25 (7.9%) | 6 (3.8%) | 7 (4.6%) | 32 (6.8%) |
| CELL DEATH | 5 (1.6%) | 0 | 3 (2.0%) | 8 (1.7%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 54 (17.0%) | 21 (13.2%) | 26 (17.1%) | 80 (17.1%) |
| ARTHRALGIA | 16 (5.0%) | 2 (1.3%) | 3 (2.0%) | 19 (4.1%) |
| BACK PAIN | 9 (2.8%) | 6 (3.8%) | 6 (3.9%) | 15 (3.2%) |
| PAIN IN EXTREMITY | 6 (1.9%) | 2 (1.3%) | 3 (2.0%) | 9 (1.9%) |
| MYALGIA | 5 (1.6%) | 2 (1.3%) | 3 (2.0%) | 8 (1.7%) |
| NECK PAIN | 3 (0.9%) | 1 (0.6%) | 4 (2.6%) | 7 (1.5%) |
| MUSCLE SPASMS | 2 (0.6%) | 0 | 3 (2.0%) | 5 (1.1%) |
| NERVOUS SYSTEM DISORDERS | 48 (15.1%) | 15 (9.4%) | 22 (14.5%) | 70 (14.9%) |
| HEADACHE | 28 (8.8%) | 6 (3.8%) | 5 (3.3%) | 33 (7.0%) |
| DIZZINESS | 7 (2.2%) | 3 (1.9%) | 5 (3.3%) | 12 (2.6%) |
| PSYCHIATRIC DISORDERS | 62 (19.6%) | 10 (6.3%) | 20 (13.2%) | 82 (17.5%) |
| INSOMNIA | 20 (6.3%) | 3 (1.9%) | 8 (5.3%) | 28 (6.0%) |
| DEPRESSION | 14 (4.4%) | 4 (2.5%) | 5 (3.3%) | 19 (4.1%) |
| ABNORMAL DREAMS | 6 (1.9%) | 0 | 3 (2.0%) | 9 (1.9%) |
| SLEEP DISORDER | 7 (2.2%) | 1 (0.6%) | 0 | 7 (1.5%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 38 (12.0%) | 9 (5.7%) | 13 (8.6%) | 51 (10.9%) |
| COUGH | 19 (6.0%) | 1 (0.6%) | 1 (0.7%) | 20 (4.3%) |
| SINUS CONGESTION | 1 (0.3%) | 0 | 4 (2.6%) | 5 (1.1%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 60 (18.9%) | 9 (5.7%) | 16 (10.5%) | 76 (16.2%) |
| RASH | 7 (2.2%) | 2 (1.3%) | 4 (2.6%) | 11 (2.3%) |
| ECZEMA | 7 (2.2%) | 1 (0.6%) | 1 (0.7%) | 8 (1.7%) |
| PRURITUS | 5 (1.6%) | 0 | 3 (2.0%) | 8 (1.7%) |

Note: Safety Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug. Adverse events are mapped according to MedDRA Version 15.

[a] Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

Table manually constructed based on the following programmed output:
Programming Details: /gf/gf2243/displays/final/code/t-teae2.sas v9.1 Output file: t-teae2.rtf1
Source: GS-US-264-0106 Week 48 CSR, Section 15.1, Table 5.1.2

**Adverse Events by Severity**

The majority of the AEs reported in Study GS-US-264-0106 were Grade 1 or 2. Grade 3 or 4 treatment-emergent AEs were reported by 5.7% of subjects in the FTC/RPV/TDF group during the study. In the SBR group, Grade 3 or 4 treatment-emergent AEs were reported by 6.9% of subjects. In the Delayed Switch group, treatment-emergent AEs were reported by 7.9% of subjects. No individual Grade 3 or 4 treatment-emergent AE occurred in greater than 1.5% of subjects in any treatment group. Grade 3 or 4 treatment-emergent AEs reported in 2 or more subjects during the study were blood creatine phosphokinase increased (2 subjects in the FTC/RPV/TDF group, 1 subject in the SBR group, and 2 subjects in the Delayed Switch group), arthralgia (2 subjects in the FTC/RPV/TDF group), depression (2 subjects in the FTC/RPV/TDF group), suicidal ideation (1 subject each in the FTC/RPV/TDF and Delayed Switch groups), and dyspnea (1 subject each in the FTC/RPV/TDF and Delayed Switch groups).

**Adverse Events Considered Related to Study Drug**

The percentage of subjects who reported an AE that was considered by the investigator to be related to study drug was similar between the FTC/RPV/TDF group (24.9%) and the Delayed Switch group (23.0%) during 48 and 24 weeks of FTC/RPV/TDF therapy, respectively. The percentage of subjects who reported an AE that was considered by the investigator to be related to study drug was low among the subjects remaining on their current ARV regimen for the first 24 weeks of the study (2.5% in the SBR group; Table 47).

The incidence of each individual study drug-related AE reported was low (< 6% in any treatment group). The most frequently reported study drug-related AEs included nausea (2.2% in the FTC/RPV/TDF group and 5.9% in the Delayed Switch group), diarrhea (3.2% in the FTC/RPV/TDF group, 0.6% in the SBR group, and 2.6% in the Delayed Switch group), and fatigue (3.5% in the FTC/RPV/TDF group). Treatment-emergent study drug-related AEs reported in at least 2 subjects are summarized in Table 47.

Most study drug-related AEs were Grade 1 in severity, and most did not require dose interruption or discontinuation of study drug. Grade 3 study drug-related AEs occurred in 1 subject each and included the following: fatigue, ALT increased, AST increased, blood creatine phosphokinase increased, decreased appetite, rhabdomyolysis, amnesia, depression, insomnia, renal impairment, and dyspnea (see description above). There were no Grade 4 treatment-emergent AEs that were considered by the investigator to be related to study drug.

**Table 47. Complera/Eviplera Study GS-US-264-0106: Treatment-Emergent Study Drug-Related Adverse Events Reported in 2 or More Subjects (Safety Analysis Set)**

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| Subjects With Any Treatment-Emergent Adverse Event Related to Study Drug | 79 (24.9%) | 4 (2.5%) | 35 (23.0%) | 114 (24.3%) |
| NAUSEA | 7 (2.2%) | 0 | 9 (5.9%) | 16 (3.4%) |
| DIARRHOEA | 10 (3.2%) | 1 (0.6%) | 4 (2.6%) | 14 (3.0%) |
| FATIGUE | 11 (3.5%) | 0 | 0 | 11 (2.3%) |
| ABNORMAL DREAMS | 6 (1.9%) | 0 | 3 (2.0%) | 9 (1.9%) |
| INSOMNIA | 7 (2.2%) | 0 | 2 (1.3%) | 9 (1.9%) |
| CELL DEATH | 4 (1.3%) | 0 | 3 (2.0%) | 7 (1.5%) |
| HEADACHE | 3 (0.9%) | 0 | 3 (2.0%) | 6 (1.3%) |
| ABDOMINAL PAIN | 2 (0.6%) | 0 | 3 (2.0%) | 5 (1.1%) |
| ALANINE AMINOTRANSFERASE INCREASED | 3 (0.9%) | 0 | 2 (1.3%) | 5 (1.1%) |
| LIVER FUNCTION TEST ABNORMAL | 4 (1.3%) | 0 | 1 (0.7%) | 5 (1.1%) |
| PROTEINURIA | 4 (1.3%) | 0 | 1 (0.7%) | 5 (1.1%) |
| SLEEP DISORDER | 5 (1.6%) | 0 | 0 | 5 (1.1%) |
| DIZZINESS | 1 (0.3%) | 0 | 3 (2.0%) | 4 (0.9%) |
| ABDOMINAL DISTENSION | 2 (0.6%) | 0 | 1 (0.7%) | 3 (0.6%) |
| ASTHENIA | 3 (0.9%) | 0 | 0 | 3 (0.6%) |
| CYTOLYTIC HEPATITIS | 1 (0.3%) | 0 | 2 (1.3%) | 3 (0.6%) |
| DECREASED APPETITE | 2 (0.6%) | 0 | 1 (0.7%) | 3 (0.6%) |
| DISTURBANCE IN ATTENTION | 3 (0.9%) | 0 | 0 | 3 (0.6%) |
| ECZEMA | 2 (0.6%) | 0 | 1 (0.7%) | 3 (0.6%) |
| FLATULENCE | 2 (0.6%) | 0 | 1 (0.7%) | 3 (0.6%) |
| AGITATION | 1 (0.3%) | 0 | 1 (0.7%) | 2 (0.4%) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 1 (0.3%) | 0 | 1 (0.7%) | 2 (0.4%) |
| BACK PAIN | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| DEPRESSION | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| DRY MOUTH | 0 | 0 | 2 (1.3%) | 2 (0.4%) |
| GASTROOESOPHAGEAL REFLUX DISEASE | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| HYPERHIDROSIS | 1 (0.3%) | 0 | 1 (0.7%) | 2 (0.4%) |
| NIGHT SWEATS | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| PARAESTHESIA | 1 (0.3%) | 0 | 1 (0.7%) | 2 (0.4%) |
| PRURITUS | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| RASH | 1 (0.3%) | 0 | 1 (0.7%) | 2 (0.4%) |
| RENAL IMPAIRMENT | 1 (0.3%) | 0 | 1 (0.7%) | 2 (0.4%) |

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| RESTLESSNESS | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| RHABDOMYOLYSIS | 0 | 0 | 2 (1.3%) | 2 (0.4%) |
| TRANSAMINASES INCREASED | 0 | 0 | 2 (1.3%) | 2 (0.4%) |
| URTICARIA | 2 (0.6%) | 0 | 0 | 2 (0.4%) |
| DYSPEPSIA | 0 | 1 (0.6%) | 1 (0.7%) | 1 (0.2%) |
| VERTIGO | 1 (0.3%) | 1 (0.6%) | 0 | 1 (0.2%) |

Note: Safety Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug. Adverse events are mapped according to MedDRA Version 15[a] Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.
Table manually constructed based on the following programmed output:
Programming Details: /gf/gf2243/displays/final/code/t-teae2.sas v9.1 Output file: t-teae2.rtf5
Source: GS-US-264-0106 CSR, Section 15.1, Table 5.1.6

## 2.1.6. Deaths

Seven subjects died during the E/C/F/TAF Phase 2 and Phase 3 studies included in this submission: 5 subjects in Studies GS-US-292-0104 and GS-US-292-0111, and 2 subjects in Study GS-US-292-0109 (Table 24). None of the events that resulted in death was considered related to study drug by the investigator.

In total, 7 subjects died during the course of the 2 Phase 3 RPV trials, 1 in the RPV group in trial C215 and 6 in the control group (3 in trial C209 and 3 in trial C215). The AEs leading to death were from a variety of causes, with some cases being associated with disease progression or HIV-related. None were assessed by the investigator as related to study medication. Only 1 of these subjects received RPV and FTC/TDF prior to death.

There were no other deaths in any study of FTC/RPV/TAF, TAF, F/TAF, E/C/F/TAF, RPV, or Complera/Eviplera included in this submission.

### 2.1.6.1. E/C/F/TAF Studies

#### 2.1.6.1.1. ART-Naive Subjects

##### 2.1.6.1.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Five subjects died (E/C/F/TAF 2 subjects, embolic stroke and alcohol poisoning; STB 3 subjects, cardiac arrest, recreational drug and alcohol overdose, and acute myocardial infarction) in Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF ISS, Listing 4). None of the SAEs that resulted in the deaths were considered related to study drugs by the investigator. Subject [redacted] in the E/C/F/TAF group in Study GS-US-292-0104 died as a result of embolic stroke that transformed into hemorrhagic stroke. Subject [redacted] in the STB group in Study GS-US-292-0104 died as a result of cardiac arrest (reported as vagally mediated bradycardic/asystole). Subject [redacted] in the E/C/F/TAF group in Study GS-US-292-0111

died on Day 90 of alcohol intoxication (reported as an SAE of alcohol poisoning on Day 90). Subject [redacted] in the STB group in Study GS-US-292-0111 died on Day 62 of acute ethanol and multiple drug toxicity (reported as an SAE of recreational drug and alcohol overdose on Day 62). Subject [redacted] in the STB group in Study GS-US-292-0111 died on Day 110 of myocardial infarction (reported as an SAE of acute myocardial infarction on Day 110, 2 weeks after the onset of an SAE of meningococcal meningitis).

2.1.6.1.2. Virologically Suppressed Subjects

2.1.6.1.2.1. Study GS-US-292-0109

Two subjects in the E/C/F/TAF group died during Study GS-US-292-0109 (Table 24; GS-US-292-0109 Week 48 CSR, Section 11.3). Subject [redacted] died on Day 148 of septic shock and Subject [redacted] died on Day 391 as a result of Stage 4 adenocarcinoma of the lung. Both events were considered by the investigator as not related to study drug.

2.1.6.2. RPV Studies

2.1.6.2.1. ART-Naive Subjects

2.1.6.2.1.1. Study C209 and C215

In total, 7 subjects died during the course of the 2 Phase 3 trials, 1 in the RPV group in trial C215 (bronchopneumonia) and 6 in the control group (3 in trial C209 [meningococcal sepsis; burkitt's lymphoma; and asphyxia] and 3 in trial C215 [cerebral toxoplasmosis and respiratory failure; dysentery; and cerebrovascular accident,]) (TMC278-C904-W96-Anal-Saf-AE/Display SAF.18). The AEs leading to death were from a variety of causes, with some cases being associated with disease progression or HIV-related. None were assessed by the investigator as related to study medication. Only 1 of these subjects received RPV and FTC/TDF prior to death (bronchopneumonia).

## 2.1.7. Other Serious Adverse Events

2.1.7.1. Summary of Other Serious Adverse Events

Serious AEs were reported for a similar percentage of subjects in both treatment groups in the comparative E/C/F/TAF studies (GS-US-292-0104, GS-US-292-0111, GS-US-292-0109) and < 10% in the E/C/F/TAF group in each study. No individual SAE occurred in ≥ 1% of subjects in either treatment group. Serious AEs were reported in Study GS-US-292-0112 for 10.7% of Cohort 1 switch subjects (n = 26), with similar percentages reported in subjects with baseline $eGFR_{CG} \geq 50$ mL/min (11.3%, n = 9) and $eGFR_{CG} < 50$ mL/min (10.5%, n = 17). SAEs were reported for 4 subjects (8.3%) in the adolescent study (Study GS-US-292-0106). The incidence of Grade 3 or 4 SAEs was low and generally similar across all E/C/F/TAF studies; few of these were reported as related to study drugs.

For subjects in the Phase 3 Week 96 pooled analysis in the FTC/TDF subset for the RPV C209 and C215 trials, SAEs were reported at similar rates to those in the overall pooled analysis. Six

(16.7%) subjects had an SAE in RPV trial C213. Only one SAE was considered treatment-related (grade 2 SAE drug hypersensitivity in 1 subject).

In the Complera/Eviplera Study GS-US-264-0111, treatment-emergent SAEs occurred in 1 subject (2.0%). Neither of the events reported for this subject was considered by the investigator to be related to study medication. In the Complera/Eviplera Study GS-US-264-0106, treatment-emergent SAEs were reported in 5.7% of subjects in the FTC/RPV/TDF group, 5.0% of subjects in the SBR group, and 5.9% of subjects in the Delayed Switch group.

2.1.7.2. E/C/F/TAF Studies

2.1.7.2.1. ART-Naive Subjects

2.1.7.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

SAEs were reported for a similar percentage of subjects in both treatment groups across Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF 8.1%, 70 subjects; STB 6.8%, 59 subjects; Table 24). Overall, the incidence of SAEs considered related to study drugs by the investigator was low and similar in both treatment groups (E/C/F/TAF 0.3%, 3 subjects; STB 0.2%, 2 subjects).

No individual SAE occurred in ≥ 1% of subjects in either treatment group. Appendicitis (E/C/F/TAF 0.5%, 4 subjects; STB 0.3%, 3 subjects) and cellulitis (E/C/F/TAF 0.1%, 1 subject; STB 0.3%, 3 subjects) were the only SAEs reported for > 2 subjects in either treatment group (E/C/F/TAF ISS, Table 14).

The SAEs that were considered related to study drugs by the investigator were staphylococcal skin infection, erythematous rash, and hypovolemic shock (for each AE: E/C/F/TAF 0.1%, 1 subject; STB 0 subjects) and immune reconstitution inflammatory syndrome and cholelithiasis (for each AE: E/C/F/TAF 0 subjects; STB 0.1%, 1 subject; E/C/F/TAF ISS, Table 15).

Three subjects had SAEs associated with renal function (E/C/F/TAF: ureteric calculus and nephrotic syndrome; STB: acute renal failure, reported as acute kidney injury); these events are described in Section 2.1.9.3.2.1.1.1.

2.1.7.2.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, similar percentages of subjects in each group (E/C/F/TAF 10.7%, 12 subjects; STB 5.2%, 3 subjects) had any SAE (Table 24; GS-US-292-0102 Week 96 CSR, Section 11.4). Depression and suicidal ideation were the only SAEs reported for > 1 subject (E/C/F/TAF 0.9%, 1 subject; STB 3.4%, 2 subjects for both events). No SAEs were considered related to study drugs by the investigator.

2.1.7.2.2. Virologically Suppressed Subjects

2.1.7.2.2.1. Study GS-US-292-0109

The SAEs were reported in Study GS-US-292-0109 for similar percentages of subjects in the 2 groups (E/C/F/TAF 4.4%, 42 subjects; FTC/TDF+3rd Agent 4.4%, 21 subjects) (Table 24; GS-US-292-0109 Week 48 CSR, Section 11.5). The following SAEs were reported for > 1 subject in either treatment group: aseptic meningitis (E/C/F/TAF 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); pneumonia (E/C/F/TAF 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); sepsis (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); sinusitis (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); chest pain (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject); diarrhea (E/C/F/TAF 0.1%; 1 subject; FTC/TDF+3rd Agent 0.4%, 2 subjects); and abdominal pain (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%).

One subject in the FTC/TDF+3rd Agent group had an SAE of acute renal failure that was considered by the investigator as related to study drugs.

2.1.7.2.2.2. Study GS-US-292-0102 Open-Label Extension

Overall, few subjects in the switch groups in Study GS-US-292-0102 had SAEs (all TDF to TAF 3.3%, 3 of 91 subjects; D/C/F/TAF to E/C/F/TAF 2.9%, 2 of 70 subjects). By PT, no SAE was reported for more than 1 subject in any switch group. No SAEs were considered related to study drugs by the investigator.

2.1.7.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.7.2.3.1. Study GS-US-292-0112

Serious AEs were reported in Study GS-US-292-0112 for 10.7% of Cohort 1 switch subjects (n = 26), with similar percentages reported in subjects with baseline $eGFR_{CG} \geq 50$ mL/min (11.3%, n = 9) and $eGFR_{CG} < 50$ mL/min (10.5%, n = 17) (GS-US-292-0112 Week 24 CSR Section 11.5).

Myocardial infarction (3 subjects) and syncope (2 subjects) were the only SAEs reported in > 1 subject. All SAEs were considered unrelated to study drugs by the investigator.

No Grade SAEs were reported for Cohort 2 ART-naive subjects.

2.1.7.2.4. ART-Naive Adolescent Subjects

2.1.7.2.4.1. Study GS-US-292-0106

The SAEs were reported for 4 subjects (8.3%) in Study GS-US-292-0106 (Table 24; GS-US-292-0106 Interim CSR, Section 11.4). With the exception of visual impairment and intermediate uveitis in Subject [redacted], no SAE was considered related to study drug by the investigator. No SAE occurred in more than 1 subject.

Visual impairment and intermediate uveitis in Subject [redacted] are noted as ocular events and described in more detail in Section 2.1.9.4.2.4.1.

2.1.7.3. RPV Studies

2.1.7.3.1. ART-Naive Subjects

2.1.7.3.1.1. Studies C209 and C215

For subjects in the Phase 3 Week 96 pooled analysis in the FTC/TDF subset, SAEs were reported at similar rates to those in the overall pooled analysis (9.5% [52 subjects] in the RPV group and 11.2% [61 subjects] in the control group). The only notable difference in incidence of SAEs between the RPV group and control group was for the PT of cholecystitis acute (0.5% [3 subjects] vs 0.0% [0 subjects], respectively). The reported SAEs were from a variety of SOCs and were comparable between treatment groups in type and incidence, and many occur commonly in HIV-infected subjects (TMC278-C904-W96-Anal-Saf-AE/Display SAF.11).

Eight subjects (1.2%) in both the RPV and control group experienced at least 1 treatment-related SAE. The following were the only PTs reported for >1 subject in either group: depression (0.3 [2 subjects] in the RPV group and 0.1% [1 subject] in the control group), suicide attempt (0.3 [2 subjects] in the RPV group and 0.0% [0 subjects] in the control group), and suicidal ideation (0.1% [1 subject] in the RPV group and 0.1% [1 subject] in the control group). While there were reports of treatment-related SAEs in the RPV groups in individual trials C209 and C215, no treatment-related SAEs were reported in the control group in trial C215.

2.1.7.3.2. ART-Naive Adolescent Subjects

2.1.7.3.2.1. Study C213

Six (16.7%) subjects were reported with an SAE in the Week 48 analysis. None of the SAEs resulted in discontinuation of the study drug. Only one SAE was considered treatment-related (grade 2 SAE drug hypersensitivity in 1 subject). The grade 2 SAE hypersensitivity was considered serious due to hospitalization, and was considered probably related to RPV and not related to the ARV regimen (TDF/3TC) by the investigator. This SAE of drug hypersensitivity was preceded by a grade 2 rash, which was treated with cetirizine and hydrocortisone. The onset of the SAE was on Day 45, when the subject was hospitalized, with a duration of 14 days. The subject recovered without ARV treatment interruption. The subject used Dapsone throughout the study since screening.

2.1.7.4. Complera/Eviplera Studies

2.1.7.4.1. Virologically Suppressed Subjects

2.1.7.4.1.1. Study GS-US-264-0111

Two treatment-emergent SAEs occurred in 1 subject (2.0%) during Study GS-US-264-0111. Neither of the events was considered by the investigator to be related to study medication (GS-US-264-0111, Section 11.4).

2.1.7.4.1.2. Study GS-US-264-0106

Treatment-emergent SAEs were reported in 5.7% of subjects in the FTC/RPV/TDF group, 5.0% of subjects in the SBR group, and 5.9% of subjects in the Delayed Switch group. Three subjects (all in the FTC/RPV/TDF group) experienced treatment-emergent SAEs that were considered by the investigator to be related to study drug. Subject [redacted] experienced a study drug-related SAE of toxic nephropathy (Grade 2) on Day 262. Study drug was continued without interruption. This SAE was ongoing at the end of the study. Subject [redacted] experienced a study drug-related SAE of renal impairment (Grade 2) on Day 60, resulting in permanent discontinuation of study drug. The SAE of renal impairment was ongoing at the end of the study. Subject [redacted] experienced a study drug-related SAE of dyspnea (Grade 3) on Day 7, resulting in permanent discontinuation of study drug. This SAE was considered to be resolved on Day 14 (GS-US-264-0106 Week 48 CSR, Section 11.4).

2.1.7.5. Phase 1 FTC/RPV/TAF Studies

There were no SAEs reported in Phase 1 studies with FTC/RPV/TAF.

2.1.7.6. Phase 1 TAF Safety Population

One SAE was reported in Phase 1 studies with TAF included in this submission. In Study GS-US-120-0104, 1 subject (Subject [redacted]) experienced chest pain considered unrelated to study drug by the investigator (GS-US-120-0104, Section 11.4).

There were no SAEs reported in Phase 1 studies with E/C/F/TAF.

## 2.1.8. Other Significant Adverse Events

2.1.8.1. Summary of Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section.

A similar percentage of subjects reported any AE between treatment groups within each randomized study. Across all studies, AEs leading to study drug discontinuation were uncommon. With longer exposures for the E/C/F/TAF group through the open-label extension of Study GS-US-292-0102, the AE profile for the E/C/F/TAF group was consistent with that in the randomized phase. Among virologically suppressed subjects in Study GS-US-292-0109, subjects who switched to E/C/F/TAF had a higher incidence of any AE considered by the investigator as

related to study drug (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects).

For subjects in the Phase 3 Week 96 pooled analysis in the FTC/TDF subset for RPV trials C209 and C215, AEs leading to discontinuation were reported at similar rates to those in the overall pooled analysis. In trial C213 in adolescents, 1 subject discontinued the study drug due to an AE (pulmonary tuberculosis, which was a mandatory withdrawal criterion).

No AEs leading to temporary or permanent study drug discontinuation occurred during Complera/Eviplera Study GS-US-264-0111, and 13 subjects permanently discontinued study drug due to a treatment-emergent AE (7 subjects [2.2%] in the FTC/RPV/TDF group and 6 subjects [3.9%] in the Delayed Switch group) in Study GS-US-264-0106.

2.1.8.2. E/C/F/TAF Studies

2.1.8.2.1. ART-Naive Subjects

2.1.8.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

The AEs that led to discontinuation of study drugs were reported for a similar percentage of subjects in either treatment group across Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF 0.9%, 8 subjects; STB 1.5%, 13 subjects; Table 24). Most AEs leading to discontinuation of study drugs were nonserious. No AE leading to discontinuation was reported for >1 subject in the E/C/F/TAF group. Three AEs leading to discontinuation were reported for > 1 subject in the STB group (vomiting, headache, and renal failure, all 0.2%, 2 subjects; E/C/F/TAF ISS, Table 16).

All AEs leading to discontinuation of study drugs were considered related to study drugs by the investigator, except those reported for the 2 subjects who died (cardiac arrest [1 subject, STB], cerebral infarction and hemorrhagic transformation stroke [1 subject, E/C/F/TAF]) and for 2 other subjects in the STB group (right and left sided anterior uveitis and spider bites, each 1 subject).

As described in Section 2.1.9.3.2.1.1.1, 4 subjects had renal AEs that resulted in discontinuation of study drugs.

2.1.8.2.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, 4 subjects (3.6%) in the E/C/F/TAF group discontinued study drug due to the following 6 AEs: neutropenia and acute promyelocytic leukemia; coxsackie viral infection; *Mycobacterium avium* complex infection; flushing and photosensitivity reaction. No subjects in the STB group discontinued study drug due to an AE.

One subject (Subject [redacted]) in the E/C/F/TAF group had 2 AEs resulting in discontinuation of study drug (flushing and photosensitivity reaction). Both were considered related to study drugs by the investigator.

No AEs leading to discontinuation of study drug were reported for the E/C/F/TAF group in the extension phase.

2.1.8.2.2. Virologically Suppressed Subjects

2.1.8.2.2.1. Study GS-US-292-0109

Few subjects in either group in Study GS-US-292-0109 discontinued study drug due to AEs (E/C/F/TAF 0.9%, 9 subjects; FTC/TDF+3rd Agent 1.5%, 7 subjects; Table 24). In the E/C/F/TAF group, no AE by PT that led to study drug discontinuation was reported for more than 1 subject. In the FTC/TDF+3rd Agent group, 3 subjects, all of whom were taking ATV/boosted+TVD regimens, had jaundice that led to study drug discontinuation.

Most of the AEs leading to discontinuation were nonserious and considered by the investigator as related to study drug.

2.1.8.2.2.2. Study GS-US-292-0102 Open-Label Extension

No subjects in the switch groups of Study GS-US-292-0102 discontinued treatment due to AEs during the extension phase.

2.1.8.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.8.2.3.1. Study GS-US-292-0112

In Study GS-US-292-0112, AEs leading to study drug discontinuation were reported for 3.3% of Cohort 1 switch subjects (n = 8), with a higher percentage reported in subjects with baseline $eGFR_{CG}$ < 50 mL/min (7.5%, n = 6) compared with subjects with baseline $eGFR_{CG} \geq 50$ mL/min (1.2%, n = 2). No individual AE leading to study drug discontinuation was reported in > 1 subject. All AEs leading to discontinuation of study drugs were considered unrelated to the study drug by the investigator, with the exception of 3 subjects (2 with baseline $eGFR_{CG}$ < 50 mL/min and 1 with baseline $eGFR_{CG} \geq 50$ mL/min; worsening of sleep disturbance, worsening renal insufficiency, and choking, respectively). Two subjects discontinued study drug due to renal AEs (Section 2.1.9.3.2.3.1.1).

No AEs leading to discontinuation of study drug were reported for Cohort 2 ART-naive subjects.

2.1.8.2.4. ART-Naive Adolescent Subjects

2.1.8.2.4.1. Study GS-US-292-0106

No subject in Study GS-US-292-0106 discontinued study drug due to an AE (Table 24).

2.1.8.3. RPV Studies

2.1.8.3.1. ART-Naive Subjects

2.1.8.3.1.1. Studies C209 and C215 (FTC/TDF Subset)

For subjects in the Phase 3 Week 96 pooled analysis in the FTC/TDF subset, AEs leading to discontinuation were reported at similar rates to those in the overall pooled analysis. The greatest differences between the treatment groups in the incidence of AEs leading to discontinuation were observed in the SOC of skin and subcutaneous tissue disorders (0.4% [2 subjects] in the RPV group vs 2.0% [11 subjects] in the control group), mostly driven by the PT rash, infections and infestations (0.5% [3 subjects] vs 1.8% [10 subjects], respectively), and psychiatric disorders (1.6% [9 subjects] vs 2.4% [13 subjects], respectively)
(TMC278-C904-W96-Anal-Saf-AE/Display Ad Hoc).

2.1.8.3.2. ART-Naive Adolescent Subjects

2.1.8.3.2.1. Study C213

One subject discontinued the study drug due to an AE (pulmonary tuberculosis, which was a mandatory withdrawal criterion). The AE was considered not related to RPV or the ARV regimen by the investigator. The onset of the AE was on Day 43 and at the time of discontinuation of the ARV treatment the AE was still ongoing with a duration of 107 days.

2.1.8.4. Complera/Eviplera Studies

2.1.8.4.1. Virologically Suppressed Subjects

2.1.8.4.1.1. Study GS-US-264-0111

No AEs leading to permanent study drug discontinuation occurred during Study GS-US-264-0111.

2.1.8.4.1.2. Study GS-US-264-0106

Thirteen subjects permanently discontinued study drug due to a treatment-emergent AE (7 subjects [2.2%] in the FTC/RPV/TDF group and 6 subjects [3.9%] in the Delayed Switch group). Of these 13 subjects, 12 subjects discontinued study drug due to an AE before Week 48 and 1 subject ([redacted] [Delayed Switch group]) discontinued study drug due to an AE that occurred after Week 48 during the extension phase. No subjects discontinued from the study due to a treatment-emergent AE while remaining on their baseline ARV regimen (SBR group). Treatment-emergent AEs of depression led to discontinuation of 2 subjects in the FTC/RPV/TDF group, and AEs of insomnia led to discontinuation of 1 subject in the FTC/RPV/TDF group and 1 subject in the Delayed Switch group. All other treatment-emergent AEs resulting in discontinuation of study drug were reported in 1 subject each .

### 2.1.8.5. Phase 1 FTC/RPV/TAF Studies

One subject permanently discontinued study drug due to an AE of colitis in Study GS-US-366-1689. Subject [redacted], a [redacted] female aged 42 years was randomized to receive FTC/RPV/TAF (Days 1 to 11), LDV/SOF+FTC/RPV/TAF (Days 12 to 22), and LDV/SOF (Days 23 to 33). On Day 12 (Day 1 of LDV/SOF+FTC/RPV/TAF treatment), the subject had a Grade 2 nonserious AE of colitis. The subject continued receiving study drug through Day 28, but discontinued on that day due to the ongoing AE of colitis. The subject was treated with ciprofloxacin, metronidazole, and mesalazine and the event resolved approximately 10 weeks after onset. The AE of colitis was considered related to LDV/SOF by the investigator.

### 2.1.8.6. Phase 1 TAF Safety Population

Discontinuations due to AEs in the E/C/F/TAF, TAF and F/TAF Phase 1 studies are summarized in Table 48. No treatment-related trends were observed regarding discontinuations due to AEs in these studies.

**Table 48. Phase 1 TAF Safety Population: Discontinuations Due to Adverse Events**

| Safety Population | Study No. | No. of Subjects Who Discontinued Due to an AE | AEs Leading to Discontinuation (No. of Subjects) | Associated Treatment and Relationship |
|---|---|---|---|---|
| E/C/F/TAF | GS-US-292-0101 | 1 | Elevated creatine phosphokinase (1) | TAF, related |
| | GS-US-292-0103 | 0 | — | — |
| | GS-US-292-0108 | 1 | Headache, urticaria, pruritus (1) | E/C/F/TAF, related |
| F/TAF | GS-US-311-0101 | 2 | Anxiety (1)<br>Joint abscess (1) | F/TAF+EVG, related<br>FTC/TAF, unrelated |
| TAF | GS-120-1101 | 0 | — | — |
| | GS-US-120-0104 | 0 | — | — |
| | GS-US-120-0107 | 0 | — | — |
| | GS-US-120-0108 | 0 | — | — |
| | GS-US-120-0109 | 0 | — | — |
| | GS-US-120-0114 | 0 | — | — |
| | | | | |
| | GS-US-120-1538 | 0 | — | — |
| | GS-US-120-1554 | 1 | Increased hepatic enzymes | RPV followed by TAF+RPV, related |

## 2.1.9. Analysis of Adverse Events by Organ System or Syndrome

### 2.1.9.1. Summary of Analysis of Adverse Events by Organ System or Syndrome

As TAF is associated with >90% lower systemic TFV exposure relative to that associated with TDF, less off-target TFV-associated toxicity was anticipated in subjects receiving E/C/F/TAF in the Phase 2 and Phase 3 randomized studies, including less impact on the nephrotoxicity and reduced BMD. Results from the Phase 2 Study GS-US-292-0102 (E/C/F/TAF) supported this, demonstrating that subjects receiving E/C/F/TAF had less impact on BMD, bone turnover biomarkers, serum creatinine, and tubular proteins (urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio) relative to those receiving STB. After the primary hypothesis of noninferior efficacy of E/C/F/TAF relative to STB was achieved in the E/C/F/TAF Phase 3 comparative studies, multiplicity adjustments were made for 4 safety endpoints with a fallback procedure in sequential order with prespecified 2-sided alpha levels: hip BMD, spine BMD, serum creatinine, and treatment-emergent proteinuria. Statistically significant differences favoring E/C/F/TAF over STB at Week 48 for all key secondary safety endpoints in ART-naive adults and virologically suppressed subjects were observed: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), change from baseline in treatment emergent proteinuria (ART-naive subjects, $p = 0.022$), and change from baseline in EFV-related symptom assessment composite score (virologically suppressed subjects; $p < 0.001$).

Small increases in serum creatinine have been observed in humans treated with RPV, likely due to inhibition of renal transporters for creatinine. However, these are not considered to be clinically important {22839}. Increases from baseline in serum creatinine levels were observed in subjects receiving FTC/RPV/TDF in both Studies GS-US-264-0111 and GS-US-264-0106 (as described below). Similar increases in creatinine were noted in the Phase 3 studies of RPV. The small mean increase in serum creatinine observed with FTC/RPV/TDF in the 2 studies is similar to that reported in the prescribing information for RPV-based regimens and is not considered to be clinically important {22839}.

Supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG. Overall, the incidence of events of interest potentially related to QT interval prolongation was low and reported with similar grades in the pooled Phase 3 trials. Too few events of interest potentially related to QT interval prolongation were reported for meaningful conclusions to be drawn concerning the time to onset and duration of these events.

Depression is an important identified risk for RPV and the RPV component of Complera/Eviplera. In the Phase 3 Week 96 pooled analysis, 4.1% of subjects with EDURANT treatment were reported with the ADR depression of at least Grade 2. Grade 3 or 4 depression was seen in 0.7% of subjects treated with EDURANT and 0.7% of controls.

### 2.1.9.2. Bone Safety

#### 2.1.9.2.1. E/C/F/TAF Studies

Bone safety was assessed in the E/C/F/TAF Phase 2 and Phase 3 studies and the Phase 3 RPV studies due to the accelerated bone loss seen in the HIV-infected population. The initiation of ART in treatment-naive HIV-infected adults is associated with a subsequent decrease in BMD in the first 12 to 24 months of use, after which BMD appears to stabilize or to show some degree of recovery. The decrease in BMD appears to be greater with TDF than with other NRTIs {11882}, {17735}, {29368}, {18854}.

#### 2.1.9.2.2. Methodology

The PTs included in the analysis of fracture events for the E/C/F/TAF studies were defined by the Gilead medical monitor in a blinded fashion prior to database lock, based on both the Standardized MedDRA Query for osteoporosis/osteopenia and on the HLGT for fractures.

In studies that enrolled adults, clinical BMD status was assessed using BMD T-scores; normal bone status was defined by a BMD T-score $\geq -1$, osteopenia by a T-score from $< -1$ to $\geq -2.5$, and osteoporosis by a T-score $< -2.5$ {16957}. Assessment of BMD Z-scores in adolescents is described in Section 2.1.9.2.2.4.1.2.

#### 2.1.9.2.2.1. ART-Naive Subjects

##### 2.1.9.2.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Bone safety is described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 48 CSR, Section 11.2.4.1; GS-US-292-0111 Week 48 CSR, Section 11.2.4.1).

###### 2.1.9.2.2.1.1.1. Fracture Events

In Studies GS-US-292-0104 and GS-US-292-0111, the incidence of fracture events was similar in both treatment groups (E/C/F/TAF 1.3%, 11 subjects; STB 1.7%, 15 subjects; E/C/F/TAF ISS, Table 24). One fracture AE in each group was reported as serious: ankle fracture (E/C/F/TAF) and thoracic vertebral fracture (STB) (E/C/F/TAF ISS, Table 14). None of the reported fracture AEs were considered by the investigator as related to the study drugs or resulted in discontinuation of study drugs.

###### 2.1.9.2.2.1.1.2. Bone Mineral Density

**Percentage Change from Baseline in Hip and Spine BMD**

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111, respectively. Statistical analysis using the fallback procedure confirmed that there were significant differences in the changes from baseline using adjusted alphas that were dependent on the results from preceding tests.

Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48; Figure 3 and Figure 4; E/C/F/TAF ISS, Tables 20.1.2 and 20.2.2). Mean (SD) baseline hip BMD values were similar for each treatment group (E/C/F/TAF 1.041 [0.1557] g/cm$^2$; STB 1.028 [0.1480] g/cm$^2$); decreases from baseline at Week 48 were as follows: E/C/F/TAF 0.657% (3.2646%), STB 2.948% (3.4095%). Mean (SD) baseline spine BMD was higher in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 1.135 [0.1759] g/cm$^2$; STB 1.114 [0.1625] g/cm$^2$; $p = 0.011$); decreases from baseline at Week 48 were as follows: E/C/F/TAF 1.301% (3.0823%), STB 2.862% (3.2460%).

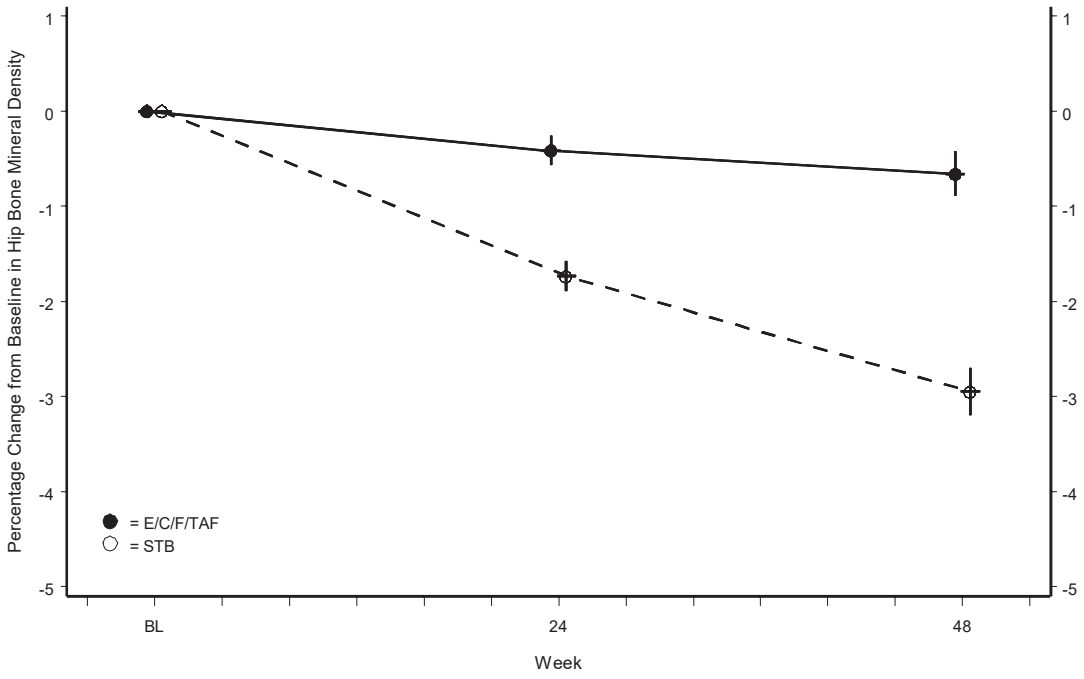
Analysis using the last observation carried forward (LOCF) method to replace missing values showed similar results to the observed data (E/C/F/TAF ISS, Tables 20.1.1 and 20.2.1).

Sensitivity analyses of percentage changes from baseline in BMD at the hip or at the spine were performed to exclude subjects who took osteoporosis medications during the study. Results were similar to those observed for all subjects in the Hip and Spine DXA Analysis Sets (GS-US-292-0104 Week 48 CSR, Section 11.2.4.1.2.1; GS-US-292-0111 Week 48 CSR, Section 11.2.4.1.2.1).

The potential for a differential effect of younger age on changes in BMD for E/C/F/TAF and STB groups was assessed in a subset of subjects aged 18 to 25 years in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102. Like children and adolescents, subjects in this age group have not yet achieved peak bone mass. In a pooled analysis of subjects 18 to 25 years of age from Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102, mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48; E/C/F/TAF ISS, Tables Req6799.1.1 and Req6799.1.2). Mean (SD) baseline hip BMD values were similar for each treatment group (E/C/F/TAF 1.073 [0.1599] g/cm$^2$; STB 1.071 [0.1562] g/cm$^2$); decreases from baseline at Week 48 were as follows: E/C/F/TAF 1.044% (3.4849%), STB 3.677% (3.3658%). Mean (SD) baseline spine BMD were similar for each treatment group (E/C/F/TAF 1.134 [0.1625] g/cm$^2$; STB 1.103 [0.1495] g/cm$^2$); decreases from baseline at Week 48 were as follows: E/C/F/TAF −1.123% (2.9321%), STB −2.597% (2.9819%). These results were similar to that observed in all ART-naive adults.

Decreased bone density was reported as a nonserious AE for 3 subjects (0.3%) in the E/C/F/TAF group and for 4 subjects (0.5%) in the STB group (E/C/F/TAF ISS, Tables 7 and 14). Decreased bone density was considered related to study drugs by the investigator for 2 subjects (0.2%) in each treatment group (E/C/F/TAF ISS, Table 11). No AEs of decreased bone density resulted in discontinuation of study drugs.

**Figure 3.** **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Hip BMD by Visit (Observed Data; Hip DXA Analysis Set)**



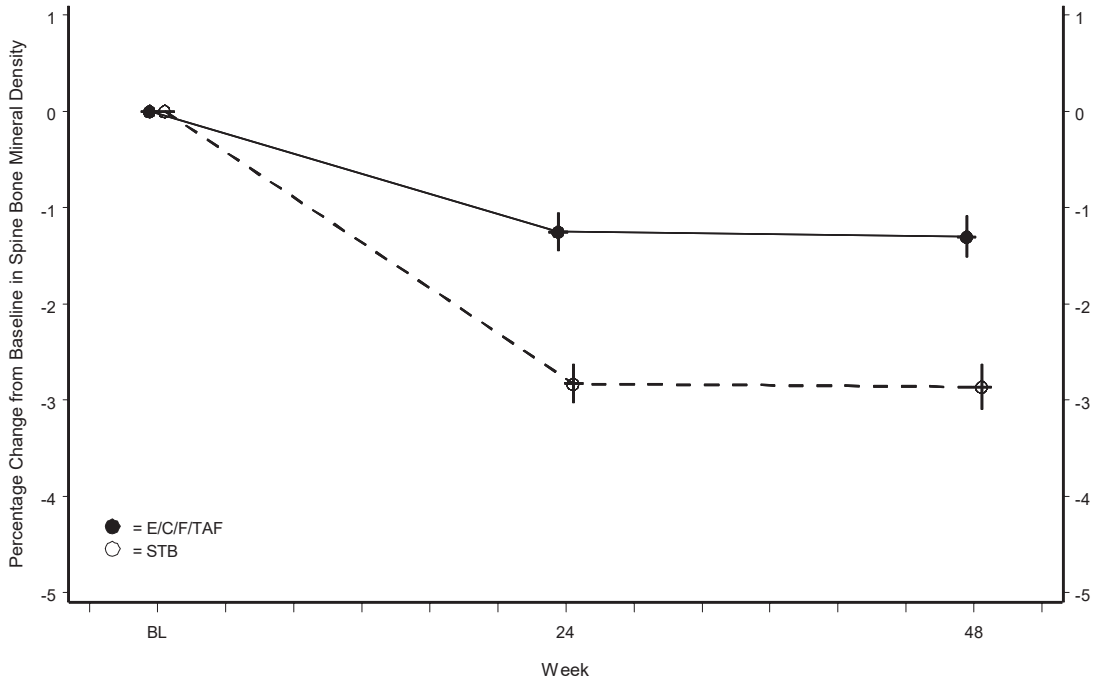

| | | | |
|---|---|---|---|
| E/C/F/TAF (n=): | 836 | 789 | 780 |
| STB (n=): | 848 | 815 | 767 |

BL = Baseline.
Only subjects with nonmissing hip BMD for the baseline visit were included in hip DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: 03SEP2014, Lab Data: 04SEP2014, s292-0111: CRF,DXA Data: 22SEP2014, Lab Data: 23SEP2014
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-hip-bmd-mn.out 26SEP2014:17:41

Source: E/C/F/TAF ISS, Figure 3.2.1

**Figure 4.** **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | |
|---|---|---|---|
| E/C/F/TAF (n=): | 845 | 797 | 784 |
| STB (n=): | 850 | 816 | 773 |

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: 03SEP2014, Lab Data: 04SEP2014, s292-0111: CRF,DXA Data: 22SEP2014, Lab Data: 23SEP2014
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out 26SEP2014:17:41

Source: E/C/F/TAF ISS, Figure 3.2.2

### *Categorical Distribution of Percentage Change from Baseline in BMD*

Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p < 0.001$ at Weeks 24 and 48). At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline in hip BMD (E/C/F/TAF 16.8%, 131 of 780 subjects; STB 50.1%, 384 of 767 subjects) and spine BMD (E/C/F/TAF 26.5%, 208 of 784 subjects; STB 45.8%, 354 of 773 subjects; E/C/F/TAF ISS, Tables 22.1 and 22.2). At Week 48, more subjects in the E/C/F/TAF group compared with the STB group had a > 3% increase from baseline in hip BMD (E/C/F/TAF 6.7%, 52 of 780 subjects; STB 3.3%, 25 of 767 subjects) and spine BMD (E/C/F/TAF 6.5%, 51 of 784 subjects; STB 2.8%, 22 of 773 subjects.

### Hip and Spine BMD Clinical Status

The distribution of the clinical BMD status at the hip or spine was similar across the 2 treatment groups at baseline (Table 49 and Table 50). The majority of subjects had normal BMD status

measured at the hip (E/C/F/TAF 77.8%, 642 of 826 subjects; STB 74.4%, 626 of 841 subjects) or the spine (E/C/F/TAF 69.8%, 583 of 835 subjects; STB 65.8%, 555 of 843 subjects). Approximately 25% to 30% of subjects had an osteopenic or osteoporotic BMD status at baseline (hip: E/C/F/TAF 22.3%, 184 of 826 subjects; STB 25.6%, 215 of 841 subjects; spine: E/C/F/TAF 30.2%, 252 of 835 subjects; STB 34.2%, 288 of 843 subjects). More subjects in both treatment groups had osteoporotic spine BMD status (E/C/F/TAF: 0.6%, 5 of 826 subjects; STB 0 subjects) compared with osteoporotic hip BMD status (E/C/F/TAF: 4.0%, 33 of 835 subjects; STB 2.7%, 23 of 843 subjects) at baseline.

The distribution of the clinical BMD status adjusted for baseline status was significantly different between treatment groups at Weeks 24 and 48 at the hip or at the spine ($p < 0.001$ at Week 24 and Week 48 for hip and spine). Based on the number of subjects with available data at Week 48, fewer subjects in the E/C/F/TAF group had worsening hip BMD clinical status from baseline (normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis) compared with the STB group (E/C/F/TAF 3.6%, 28 of 768 subjects; STB 7.5%, 57 of 761 subjects). Similarly, fewer subjects in the E/C/F/TAF group had worsening spine BMD clinical status at Week 48 compared with the STB group (E/C/F/TAF 8.0%, 60 of 747 subjects; STB 12.5%, 93 of 746 subjects).

**Table 49. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Clinical Hip BMD Status at Baseline and Week 48 (Hip DXA Analysis Set)**

| | E/C/F/TAF (N=836) Baseline | | | | STB (N=848) Baseline | | | | E/C/F/TAF vs STB p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Normal (N=642) | Osteopenia (N=179) | Osteoporosis (N=5) | Missing (N=10) | Normal (N=626) | Osteopenia (N=215) | Osteoporosis (N=0) | Missing (N=7) | |
| At Week 48 | | | | | | | | | |
| Normal | 575 (95.8%) | 14 (8.3%) | 0 | 4 | 509 (90.4%) | 8 (4.0%) | 0 | 2 | <.001 |
| Osteopenia | 24 (4.0%) | 151 (89.9%) | 0 | 0 | 54 (9.6%) | 187 (94.4%) | 0 | 1 | |
| Osteoporosis | 1 (0.2%) | 3 (1.8%) | 5 (100.0%) | 0 | 0 | 3 (1.5%) | 0 | 1 | |
| Missing | 42 | 11 | 0 | 6 | 63 | 17 | 0 | 3 | |

The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.
Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.
Clinical BMD Status is defined based on T-score, where Normal: >= −1.0; Osteopenia: >= −2.5 to < −1.0; Osteoporosis: < −2.5.
P-value was from rank analysis of covariance adjusting for baseline clinical status for treatment comparison.
Due to age limitation, some subjects had BMD values, but no T-score to define clinical status.
Source: E/C/F/TAF ISS, Table 21.1

**Table 50. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Clinical Spine BMD Status at Baseline and Week 48 (Spine DXA Analysis Set)**

| | E/C/F/TAF (N=845) Baseline | | | | STB (N=850) Baseline | | | | E/C/F/TAF vs STB p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Normal (N=583) | Osteopenia (N=219) | Osteoporosis (N=33) | Missing (N=10) | Normal (N=555) | Osteopenia (N=265) | Osteoporosis (N=23) | Missing (N=7) | |
| At Week 48 | | | | | | | | | |
| Normal | 493 (91.1%) | 14 (6.8%) | 0 | 2 | 428 (85.3%) | 5 (2.0%) | 0 | 2 | <.001 |
| Osteopenia | 48 (8.9%) | 180 (87.4%) | 3 (10.0%) | 2 | 74 (14.7%) | 220 (90.2%) | 2 (9.5%) | 1 | |
| Osteoporosis | 0 | 12 (5.8%) | 27 (90.0%) | 0 | 0 | 19 (7.8%) | 19 (90.5%) | 1 | |
| Missing | 42 | 13 | 3 | 6 | 53 | 21 | 2 | 3 | |

The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.
Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.
Clinical BMD Status is defined based on T-score, where Normal: >= −1.0; Osteopenia: >= −2.5 to < −1.0; Osteoporosis: < −2.5.
P-value was from rank analysis of covariance adjusting for baseline clinical status for treatment comparison.
Due to age limitation, some subjects had BMD values, but no T-score to define clinical status.
Source: E/C/F/TAF ISS, Table 21.2

The incidences of osteopenia and osteoporosis reported as an AE were as follows: osteopenia: E/C/F/TAF 3.7 %, 32 subjects; STB 5.1%, 44 subjects; osteoporosis: E/C/F/TAF 1.3%, 11 subjects; STB 1.5%, 13 subjects (E/C/F/TAF ISS, Table 7). Osteopenia was considered related to study drugs by the investigator for 25 subjects: E/C/F/TAF 8 subjects (0.9%), STB 17 subjects (2.0%); osteoporosis was considered related to study drugs by the investigator for 7 subjects: E/C/F/TAF 3 subject (0.3%), STB 4 subjects (0.5%) (E/C/F/TAF ISS, Table 11). Nineteen of the 32 subjects in the E/C/F/TAF group and 18 of the 44 subjects in the STB group who had AEs of osteopenia were reported prior to Day 30 (GS-US-292-0104 Week 48 CSR, Appendix 16.2, Listing 17; GS-US-292-0111 Week 48 CSR, Appendix 16.2, Listing 17). Nine of the 11 subjects in the E/C/F/TAF group and 8 of the 13 subjects in the STB group who had AEs of osteoporosis were reported prior to Day 30. The reporting of these events was temporally related to the baseline DXA scan. All AEs of osteopenia or osteoporosis were nonserious, and none resulted in discontinuation of study drugs (E/C/F/TAF ISS, Tables 14 and 16).

#### 2.1.9.2.2.1.1.3. Bone Laboratory Parameters

Increases from baseline in the bone turnover biomarkers C-telopeptide (bone resorption biomarker) and procollagen type 1 N-terminal propeptide (P1NP; bone formation), as well as PTH, a hormone involved in bone metabolism, were smaller in the E/C/F/TAF group compared with the STB group at both Weeks 24 and 48 ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline; E/C/F/TAF ISS, Tables 23.1, 23.2, and 23.3). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows: C-telopeptide: E/C/F/TAF 9.1% (−9.4%, 32.7%), STB 21.1% (0.0%, 44.6%); P1NP: E/C/F/TAF 26.86% (3.42%, 60.18%), STB 72.85% (41.28%, 120.58%); PTH: E/C/F/TAF 23.0% (−4.5%, 58.7%), STB 41.9% (8.9%, 88.0%).

### 2.1.9.2.2.1.2. Study GS-US-292-0102

Bone safety for Study GS-US-292-0102 is described in detail in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.2.4.1).

#### 2.1.9.2.2.1.2.1. Fracture Events

In the randomized phase of Study GS-US-292-0102, 1 subject in the E/C/F/TAF group and 2 subjects in the STB group had a fracture event (E/C/F/TAF: pelvic fracture, upper limb [arm] fracture, STB: thoracic vertebral fracture, ankle fracture). Pelvic fracture, upper limb fracture (both in 1 subject), and thoracic vertebral fracture (1 subject) were serious, while the ankle fracture (1 subject) was nonserious. All reported fracture AEs were the result of trauma, considered by the investigator as unrelated to the study drugs, and none resulted in discontinuation of study drugs.

#### 2.1.9.2.2.1.2.2. Bone Mineral Density

**Percentage Change from Baseline in Hip and Spine BMD**

In the randomized phase of Study GS-US-292-0102, decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the

differences between the 2 groups in mean percentage changes from baseline in hip or spine BMD at Weeks 24 and 48; Figure 5 and Figure 6). Mean (SD) percentage decreases from baseline in hip BMD were as follows:

- At Week 24: E/C/F/TAF 0.42% (1.678), STB 2.02% (2.664)
- At Week 48: E/C/F/TAF 0.67% (2.180), STB 3.12% (3.367)

Mean (SD) percentage decreases from baseline in spine BMD were as follows:

- At Week 24: E/C/F/TAF 0.93% (2.965), STB 2.55% (2.507)
- At Week 48: E/C/F/TAF 1.02% (3.447), STB 3.24% (3.219)

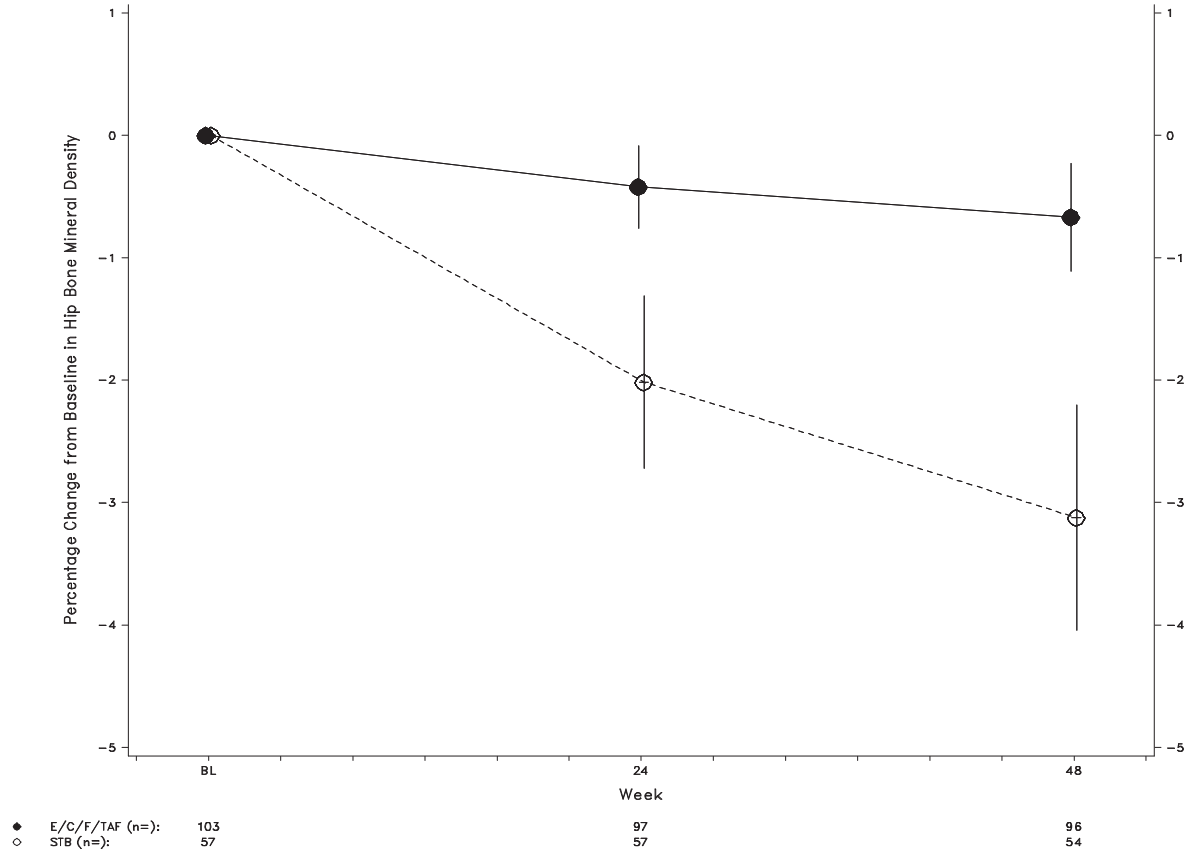
Analysis using LOCF to replace missing values showed similar results to the observed data for the randomized phase.

In the E/C/F/TAF group at Week 96, mean (SD) percentage decreases from baseline in hip or spine BMD were consistent with results at Week 48, as follows: hip 0.78% (2.452%); spine 0.71% (3.697%).

In the randomized phase, differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p < 0.001$ for both parameters at Weeks 24 and 48). At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline in both hip (E/C/F/TAF 11.5%, STB 44.4%) and spine BMD (E/C/F/TAF 24.3%, STB 53.6%).

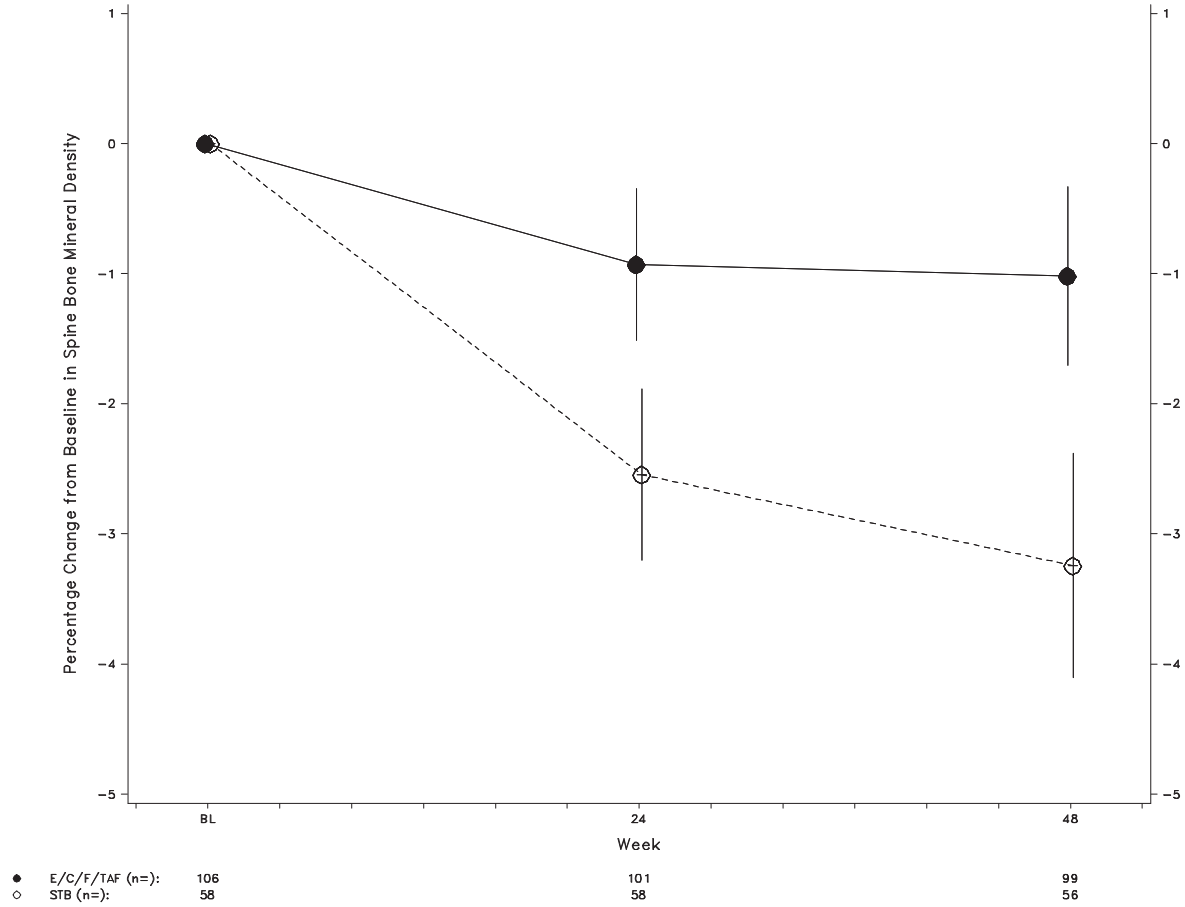
In the E/C/F/TAF group at Week 96, the categorical distributions of percentage change from baseline in hip or spine BMD were consistent with results at Week 48.

**Figure 5.** **E/C/F/TAF Study GS-US-292-0102: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)**




Source: GS-US-292-0102 Week 48 CSR, Section 15.1, Figure Req6660.1.1

**Figure 6. E/C/F/TAF Study GS-US-292-0102: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)**




Source: GS-US-292-0102 Week 48 CSR, Section 15.1, Figure Req6660.2.1

### *Hip and Spine BMD Clinical Status*

In the randomized phase of Study GS-US-292-0102, few subjects in either group had worsening hip or spine BMD clinical status (at Week 48: hip: E/C/F/TAF 3.3%, 3 subjects; STB 9.3%, 5 subjects; spine: E/C/F/TAF 7.4%, 7 subjects; STB 7.1%, 4 subjects).

In the E/C/F/TAF group at Week 96, the numbers of subjects with shifts in hip or spine BMD clinical status were consistent with results at Week 48.

#### 2.1.9.2.2.1.2.3. Bone Laboratory Parameters

In the randomized phase of Study GS-US-292-0102, increases from baseline in the bone biomarkers C-telopeptide and P1NP were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline at Weeks 24 and 48).

Serum bone specific alkaline phosphatase and osteocalcin were only measured at Week 24; results were consistent with those for C-telopeptide and P1NP at this time point.

In the E/C/F/TAF group at Week 96, median percentage changes from baseline in P1NP and C-telopeptide were consistent with results at Week 48.

2.1.9.2.2.2. Virologically Suppressed Subjects

2.1.9.2.2.2.1. Study GS-US-292-0109

Bone safety for Study GS-US-292-0109 is described in detail in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.2.4.1).

2.1.9.2.2.2.1.1. Fracture Events

The percentages of subjects in each group of Study GS-US-292-0109 who had a fracture event were comparable (E/C/F/TAF 1.5%, 14 subjects; FTC/TDF+3rd Agent 0.6%, 3 subjects; $p = 0.20$). In the E/C/F/TAF group 3 fractures were reported as SAEs: skull fracture (Subject [redacted]), radius fracture (Subject [redacted]), and hip fracture (Subject [redacted]). All the other fracture events reported for subjects in both groups were nonserious. All reported fracture AEs were the result of trauma and considered by the investigator as unrelated to the study drugs; none were indicative of fragility fractures, and none resulted in permanent discontinuation of study drugs.

2.1.9.2.2.2.1.2. Bone Mineral Density

**Percentage Change from Baseline in Hip and Spine BMD**

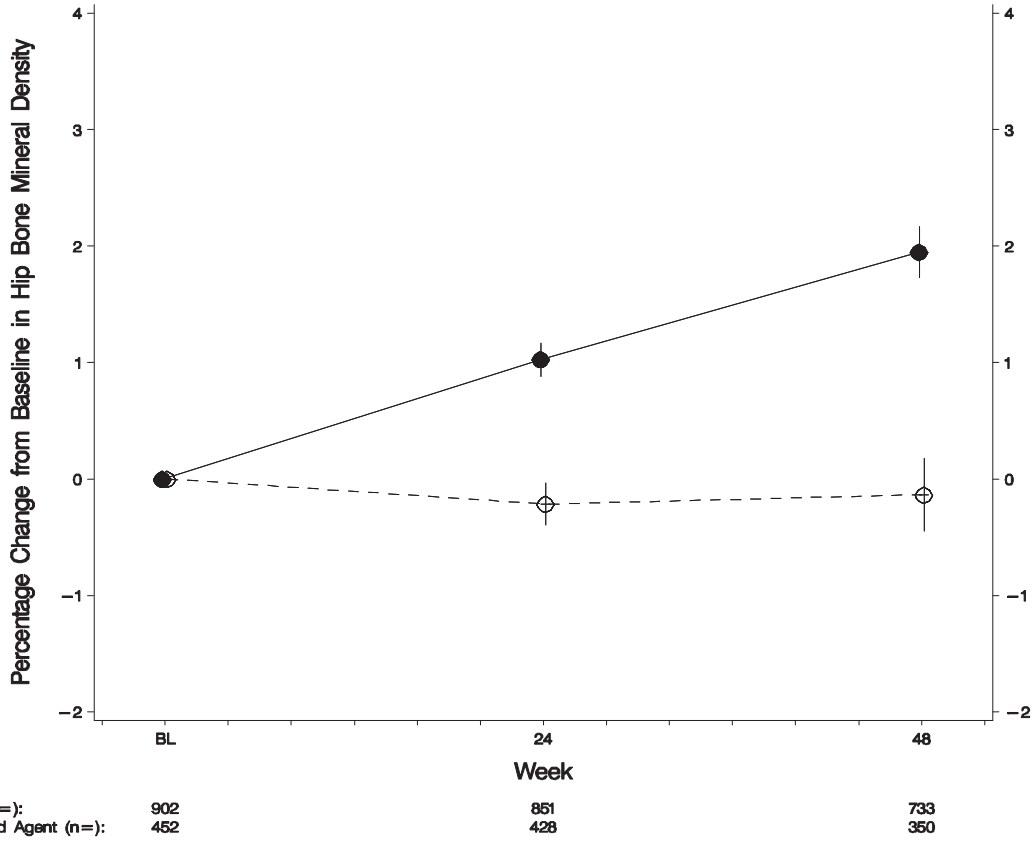
The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for Study GS-US-292-0109, respectively. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests. There were increases from baseline in mean (SD) BMD at the hip or at the spine in the E/C/F/TAF group as compared with minimal changes from baseline in both parameters in the FTC/TDF+3rd Agent group at both Weeks 24 and 48 ($p < 0.001$ for the differences between groups; Figure 7 and Figure 8).

Mean (SD) percentage changes from baseline in BMD at Week 48 were as follows:

- Hip: E/C/F/TAF 1.949% (2.9956); FTC/TDF+3rd Agent −0.136% (2.9890)
- Spine: E/C/F/TAF 1.861% (3.0889); FTC/TDF+3rd Agent −0.110% (3.7415)

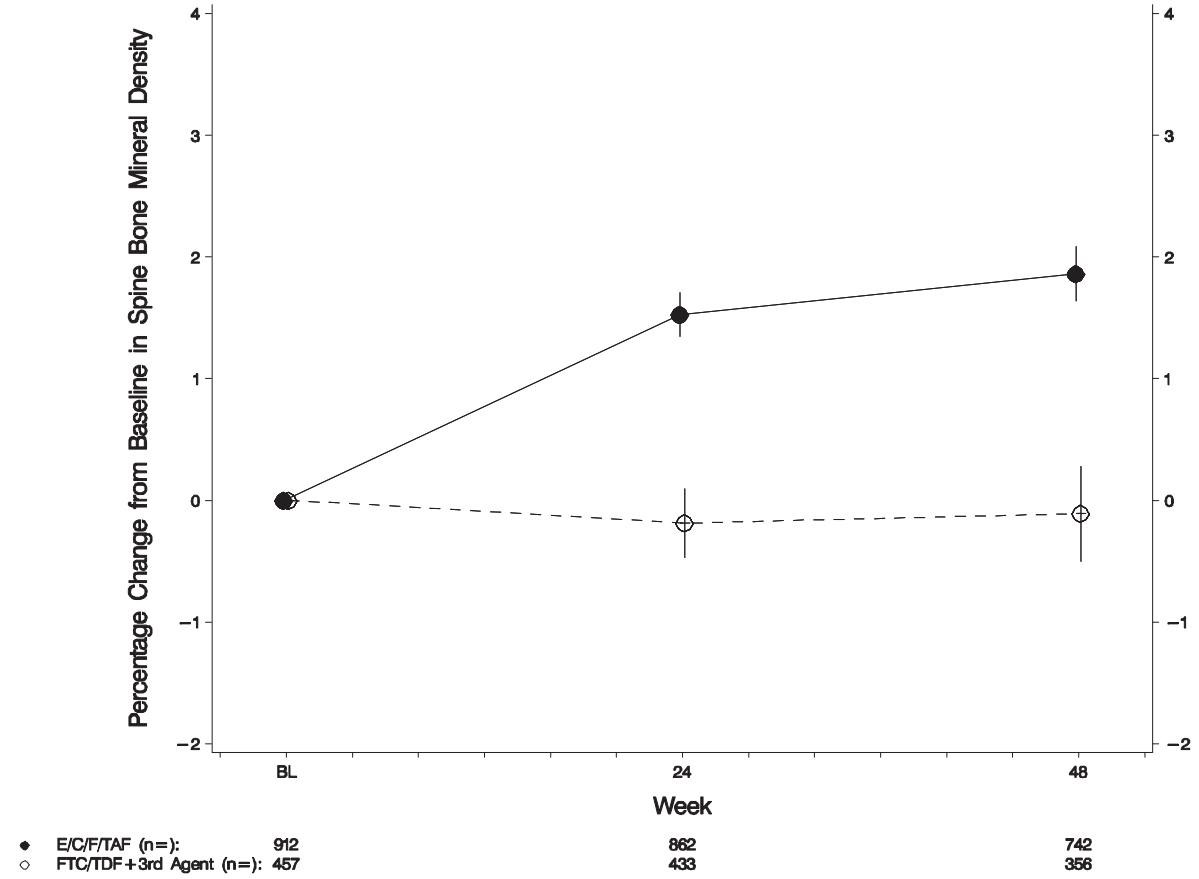
Similar results were obtained when the data were analyzed using the LOCF approach for the Week 48 Hip and Spine DXA Analysis Sets.

**Figure 7.** **E/C/F/TAF Study GS-US-292-0109: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)**




Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Figure 8.2.1

**Figure 8.** **E/C/F/TAF Study GS-US-292-0109: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)**




Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Figure 8.2.2

***Percentage Change from Baseline in Hip and Spine BMD by Prior Treatment Subgroup***

An increase from baseline in BMD was consistently observed for subjects in the E/C/F/TAF group at the hip or at the spine at Weeks 24 and 48, regardless of prior treatment regimen. In contrast, there were minimal changes from baseline in both parameters for subjects who continued on their baseline regimen. Significant differences between the E/C/F/TAF and FTC/TDF+3rd Agent groups were observed at Weeks 24 and 48 for the percentage changes from baseline in hip or spine BMD in each subgroup by prior treatment ($p < 0.001$).

Mean (SD) percentage changes from baseline in hip BMD at Week 48 by prior treatment group were as follows:

- STB: E/C/F/TAF 1.622% (3.0016); FTC/TDF+3rd Agent 0.014% (3.1113); difference in least-squares mean (LSM): 1.609%, 95% CI: 0.949% to 2.268%

- ATR: E/C/F/TAF 2.398% (3.3332); FTC/TDF+3rd Agent 0.035% (2.8713); difference in LSM: 2.363%, 95% CI: 1.607% to 3.118%

- ATV/boosted+TVD: E/C/F/TAF 1.883% (2.6358); FTC/TDF+3rd Agent −0.415% (2.9637); difference in LSM: 2.298%, 95% CI: 1.715% to 2.882%

Mean (SD) percentage changes from baseline in spine BMD at Week 48 by prior treatment group were as follows:

- STB: E/C/F/TAF 1.735% (2.9805); FTC/TDF+3rd Agent −0.276% (3.1363); difference in LSM 2.011%, 95% CI: 1.353% to 2.669%

- ATR: E/C/F/TAF 1.686% (3.3176); FTC/TDF+3rd Agent 0.059% (3.3071); difference in LSM 1.626%, 95% CI: 0.858% to 2.395%

- ATV/boosted+TVD: E/C/F/TAF 2.127% (2.9818); FTC/TDF+3rd Agent −0.091% (4.5460); difference: in LSM 2.218%, 95% CI: 1.465% to 2.971%

Similar results were obtained when the data in each subgroup by prior treatment were analyzed using the LOCF approach for the Week 48 Hip and Spine DXA Analysis Sets.

***Percentage Change from Baseline in Hip and Spine BMD by Osteoporosis Medication Use***

Similar percentages of subjects in each treatment group were taking osteoporosis medications at study entry (E/C/F/TAF 8.7%, 83 subjects; FTC/TDF+3rd Agent 8.0%, 38 subjects). During the study, 7.4% (n = 71) of subjects in the E/C/F/TAF group and 4.0% (n = 19) of subjects in the FTC/TDF+3rd Agent group initiated osteoporosis medications.

***Categorical Distribution of Percentage Change from Baseline in BMD***

Differences between the 2 treatment groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p < 0.001$ for both parameters at Weeks 24 and 48.

Higher percentages of subjects in the E/C/F/TAF group had increases from baseline in BMD of > 3% relative to the FTC/TDF+3rd Agent group at Week 24 (hip: E/C/F/TAF 12.0%; FTC/TDF+3rd Agent 2.8%; spine: E/C/F/TAF 28.2%, FTC/TDF+3rd Agent 11.1%) and at Week 48 (hip: E/C/F/TAF 25.2%; FTC/TDF+3rd Agent 8.6%; spine: E/C/F/TAF 33.6%, FTC/TDF+3rd Agent 13.8%; Table 51).

Smaller percentages of subjects in the E/C/F/TAF group had decreases from baseline in BMD of > 3% relative to the FTC/TDF+3rd Agent group at Week 24 (hip: E/C/F/TAF 1.3%, FTC/TDF+3rd Agent 6.5%; spine: E/C/F/TAF 4.6%, FTC/TDF+3rd Agent 14.3%) and at Week 48 (hip: E/C/F/TAF 1.9%; FTC/TDF+3rd Agent 11.1%; spine: E/C/F/TAF 5.8%, FTC/TDF+3rd Agent 17.4%).

**Table 51. E/C/F/TAF Study GS-US-292-0109: Percentage of Subjects with > 3% Change in Hip and Spine BMD by Visit (Hip and Spine DXA Analysis Sets)**

| Percentage Change | Visit | E/C/F/TAF n/N (%) | FTC/TDF+3rd Agent n/N (%) |
|---|---|---|---|
| **Hip BMD[a]** | | | |
| > 3% Decrease | Week 24 | 11/851 (1.3%) | 28/428 (6.5%) |
| | Week 48 | 14/733 (1.9%) | 39/350 (11.1%) |
| > 3% Increase | Week 24 | 102/851 (12.0%) | 12/428 (2.8%) |
| | Week 48 | 185/733 (25.2%) | 30/350 (8.6%) |
| **Spine BMD[b]** | | | |
| > 3% Decrease | Week 24 | 40/862 (4.6%) | 62/433 (14.3%) |
| | Week 48 | 43/742 (5.8%) | 62/356 (17.4%) |
| > 3% Increase | Week 24 | 243/862 (28.2%) | 48/433 (11.1%) |
| | Week 48 | 249/742 (33.6%) | 49/356 (13.8%) |

a The Hip DXA Analysis Set is defined as subjects who received at least 1 dose of study drug and had nonmissing hip BMD for the baseline visit.
b The Spine DXA Analysis Set is defined as subjects who received at least 1 dose of study drug and had nonmissing spine BMD for the baseline visit.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 43.1 and 43.2

### Hip and Spine BMD Clinical Status

The majority of subjects in both treatment groups had normal hip and spine BMD clinical status at baseline and retained that status at Week 24 and Week 48.

The distribution of the clinical BMD status adjusted for baseline status was significantly different between treatment groups at Weeks 24 and 48 at the hip ($p \leq 0.002$) or at the spine ($p \leq 0.002$). Based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had an improvement in hip BMD clinical status (E/C/F/TAF 5.6%, 41 of 733 subjects; FTC/TDF+3rd Agent 2.0%, 7 of 350 subjects), and a lower percentage of subjects in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening hip BMD clinical status (E/C/F/TAF 0.7%, 5 subjects; FTC/TDF+3rd Agent 4.3%, 15 subjects).

Similarly, based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had an improvement in spine BMD clinical status (E/C/F/TAF 7.5%, 56 of 742 subjects; FTC/TDF+3rd Agent 3.7%, 13 of 356 subjects) and a lower percentage of subjects in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening spine BMD clinical status (E/C/F/TAF 0.9%, 7 subjects; FTC/TDF+3rd Agent 5.1%, 18 subjects).

#### 2.1.9.2.2.2.1.3. Bone Laboratory Parameters

There was a decrease from baseline in serum levels of the bone formation biomarker P1NP and also in PTH, involved in bone formation and resorption, in the E/C/F/TAF group as compared with an increase from baseline in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). There was no change from baseline in serum levels of the bone resorption biomarker C-telopeptide in the E/C/F/TAF group compared with an increase from baseline in the FTC/TDF+3rd Agent at Week 48 ($p = 0.007$ for the difference between groups).

Median (Q1, Q3) percentage changes from baseline in P1NP, C-telopeptide, and PTH at Week 48 were as follows:

- P1NP: E/C/F/TAF −26.89% (−41.41, −10.63); FTC/TDF+3rd Agent 4.48% (−12.54, 25.36)
- C-telopeptide: E/C/F/TAF 0.0% (−16.0, 18.2); FTC/TDF+3rd Agent 2.9% (−10.0, 22.6)
- PTH: E/C/F/TAF −3.3% (−24.6, 21.7); FTC/TDF+3rd Agent 7.1% (−12.6, 39.4)

### 2.1.9.2.2.2.2. Study GS-US-292-0102 Open-Label Extension

#### 2.1.9.2.2.2.2.1. Fracture Events

Two subjects in the DRV+COBI+TVD to E/C/F/TAF group had a fracture event (ankle fracture, hand [finger] fracture) during the extension phase. The hand (finger) fracture (Subject [redacted]) was nonserious while the ankle fracture (Subject [redacted]) was serious; both events were traumatic, considered by the investigator as unrelated to the study drug, and no action was taken with study drug as a result of either event.

#### 2.1.9.2.2.2.2.2. Bone Mineral Density

**Percentage Change from Baseline in Hip and Spine BMD**

In contrast to the ART-naive population, increases from baseline in hip or spine BMD were observed at Week 24 of the extension phase in the all TDF to TAF switch group. The mean (SD) percentage increases from baseline in hip or spine BMD at Week 24 were 0.58% (1.963) and 1.18% (3.426), respectively. In the D/C/F/TAF to E/C/F/TAF group, the mean (SD) percentage changes from baseline in BMD at Week 24 of the extension phase were 0.22% (2.467) at the hip and 0.71% (3.930).

A majority of subjects in the all TDF to TAF group had increases from baseline in BMD at Week 24 of the extension phase (hip: 62.6%; spine: 68.2%; Table 52 and Table 53). Few subjects in this switch group had > 3% decrease from baseline in hip BMD (1.6%) or spine BMD (7.5%).

**Table 52. E/C/F/TAF Study GS-US-292-0102: Categorical Distribution of Changes in Hip BMD at Week 24 of the Extension Phase (All E/C/F/TAF Hip DXA Analysis Set)**

| Percentage Change at Week 24 | All TDF to TAF (N=87) | STB to E/C/F/TAF (N=52) | DRV+COBI+TVD to E/C/F/TAF (N=35) | D/C/F/TAF to E/C/F/TAF (N=68) |
|---|---|---|---|---|
| > 5% Decrease | 0/64 | 0/51 | 0/13 | 1/31 (3.2%) |
| > 3 to <= 5% Decrease | 1/64 (1.6%) | 1/51 (2.0%) | 0/13 | 0/31 |
| > 1 to <= 3% Decrease | 13/64 (20.3%) | 11/51 (21.6%) | 2/13 (15.4%) | 8/31 (25.8%) |
| > 0 to <= 1% Decrease | 10/64 (15.6%) | 7/51 (13.7%) | 3/13 (23.1%) | 5/31 (16.1%) |
| >=0 to <= 1% Increase | 17/64 (26.6%) | 11/51 (21.6%) | 6/13 (46.2%) | 6/31 (19.4%) |
| > 1 to <= 3% Increase | 17/64 (26.6%) | 16/51 (31.4%) | 1/13 (7.7%) | 9/31 (29.0%) |
| > 3 to <= 5% Increase | 3/64 (4.7%) | 2/51 (3.9%) | 1/13 (7.7%) | 1/31 (3.2%) |
| > 5% Increase | 3/64 (4.7%) | 3/51 (5.9%) | 0/13 | 1/31 (3.2%) |

Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 37.3.1.2

**Table 53. E/C/F/TAF Study GS-US-292-0102: Categorical Distribution of Changes in Spine BMD at Week 24 of the Extension Phase (All E/C/F/TAF Spine DXA Analysis Set)**

| Percentage Change at Week 24 | All TDF to TAF (N=89) | STB to E/C/F/TAF (N=53) | DRV+COBI+TVD to E/C/F/TAF (N=36) | D/C/F/TAF to E/C/F/TAF (N=69) |
|---|---|---|---|---|
| > 5% Decrease | 2/66 (3.0%) | 2/53 (3.8%) | 0/13 | 3/31 (9.7%) |
| > 3 to <= 5% Decrease | 3/66 (4.5%) | 2/53 (3.8%) | 1/13 (7.7%) | 1/31 (3.2%) |
| > 1 to <= 3% Decrease | 9/66 (13.6%) | 6/53 (11.3%) | 3/13 (23.1%) | 7/31 (22.6%) |
| > 0 to <= 1% Decrease | 7/66 (10.6%) | 4/53 (7.5%) | 3/13 (23.1%) | 0/31 |
| >=0 to <= 1% Increase | 11/66 (16.7%) | 11/53 (20.8%) | 0/13 | 5/31 (16.1%) |
| > 1 to <= 3% Increase | 16/66 (24.2%) | 12/53 (22.6%) | 4/13 (30.8%) | 5/31 (16.1%) |
| > 3 to <= 5% Increase | 12/66 (18.2%) | 10/53 (18.9%) | 2/13 (15.4%) | 8/31 (25.8%) |
| > 5% Increase | 6/66 (9.1%) | 6/53 (11.3%) | 0/13 | 2/31 (6.5%) |

Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 37.3.2.2

### Hip and Spine BMD Clinical Status

At Week 24 of the extension phase, few subjects in the switch groups had shifts in hip or spine BMD clinical status.

#### 2.1.9.2.2.2.2.3. Bone Laboratory Parameters

In the all TDF to TAF group, median percentage decreases from baseline were observed for the bone biomarkers serum C-telopeptide and serum P1NP at Week 24 of the extension phase. Serum bone specific alkaline phosphatase and osteocalcin were not measured for the switch groups during the extension phase.

### 2.1.9.2.2.3. Subjects with Mild to Moderate Renal Impairment

#### 2.1.9.2.2.3.1. Study GS-US-292-0112

Bone safety for Study GS-US-292-0112 is described in detail in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.3.4.1).

##### 2.1.9.2.2.3.1.1. Fracture Events

A total of 5 subjects (2.1%) experienced 6 fracture events, of whom 4 were subjects with pre-switch TDF use and 1 was a subject without pre-switch TDF use. All reported fracture AEs were considered unrelated to study drug by the investigator and none resulted in discontinuation of study drug. One fracture event (spinal compression fracture) was serious. All fracture events were the result of trauma, and none were reported as fragility fractures.

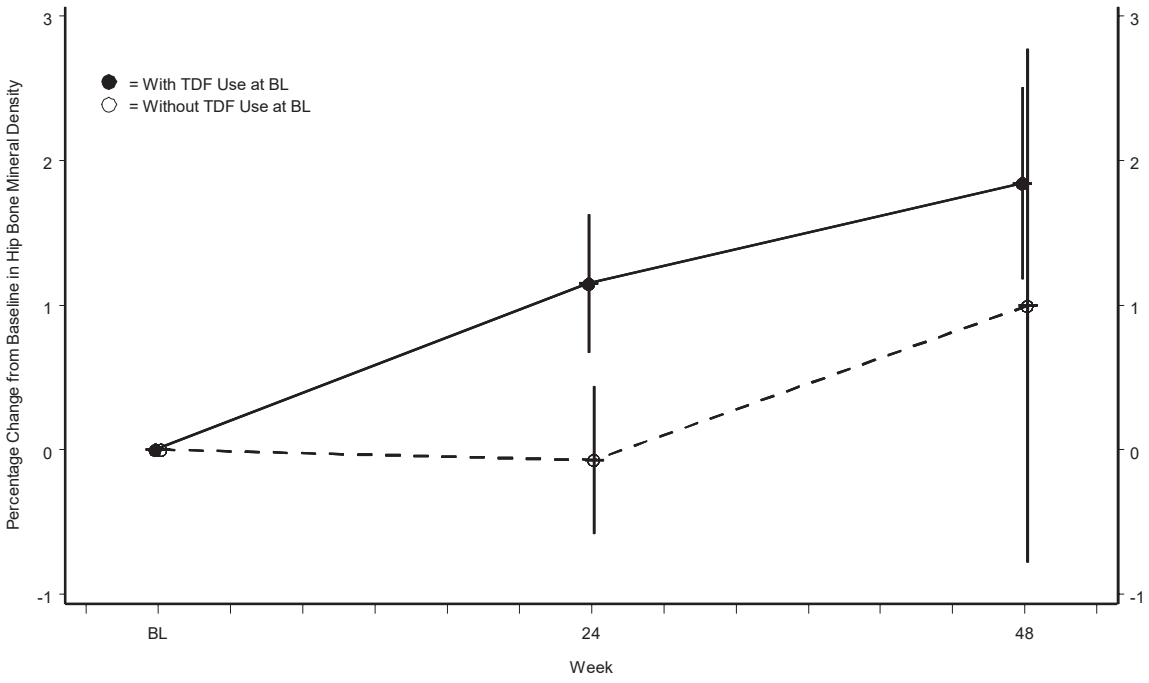
No fracture events occurred in Cohort 2 ART-naive subjects.

##### 2.1.9.2.2.3.1.2. Bone Mineral Density

**Percentage Change from Baseline in Hip and Spine BMD**

Overall, hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF. Mean (SD) percentage increases from baseline were observed in hip BMD (Week 24: 0.733% [2.7674]; Week 48: 1.575% [4.5738]) and spine BMD (Week 24: 1.643% [3.6250]; Week 48: 2.368 % [4.2582]; Figure 9 and Figure 10). Mean percentage changes from baseline in hip and spine BMD for those with pre-switch TDF use compared with those without pre-switch TDF use were 1.151% versus −0.071% for hip BMD and 2.370% versus 0.291% for spine BMD at Week 24 and 1.843% versus 0.997% for hip BMD and 2.994% versus 1.104% for spine BMD at Week 48.

**Figure 9. E/C/F/TAF Study GS-US-292-0112: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)**



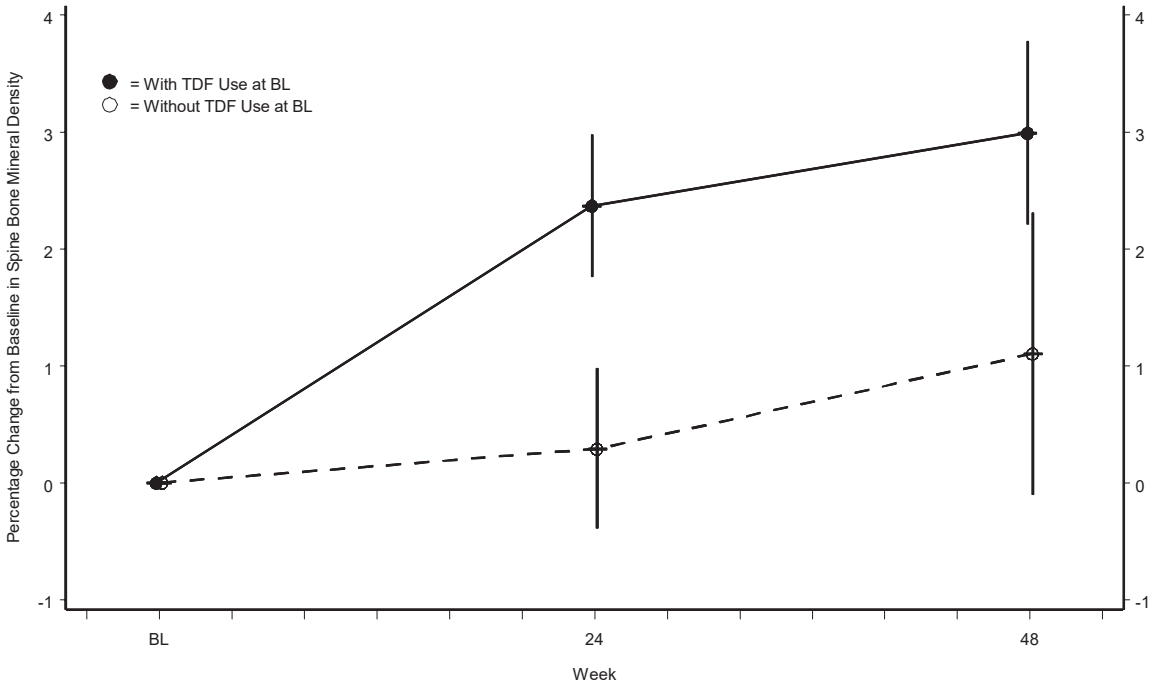

| | | | |
|---|---|---|---|
| With TDF Use at BL (n=): | 154 | 148 | 110 |
| Without TDF Use at BL (n=): | 82 | 77 | 51 |

BL = Baseline.
Only subjects with nonmissing baseline hip BMD value were included in hip DXA analysis set.

Data Extracted: CRF Data: 17SEP2014, Lab Data: 19SEP2014, Dexa Data: 18SEP2014
Source: .../version1/prog/t-dexa-bmd.sas v9.2 Output file: g-dexa-hip-bmd-mean.out 20SEP2014:10:37

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Figure 22.1.2

**Figure 10. E/C/F/TAF Study GS-US-292-0112: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | |
|---|---|---|---|
| With TDF Use at BL (n=): | 154 | 147 | 107 |
| Without TDF Use at BL (n=): | 82 | 79 | 53 |

BL = Baseline.
Only subjects with nonmissing baseline spine BMD value were included in spine DXA analysis set.

Data Extracted: CRF Data: 17SEP2014, Lab Data: 19SEP2014, Dexa Data: 18SEP2014
Source: .../version1/prog/t-dexa-bmd.sas v9.2 Output file: g-dexa-spine-bmd-mean.out 20SEP2014:10:37

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Figure 22.2.2

There was evidence for an improvement in hip and spine BMD after switch to E/C/F/TAF. When assessed using a threshold of 3% for changes from baseline, higher percentages of subjects had increases versus decreases from baseline in BMD at both the hip (Week 24: 13.8% versus 7.2%; Week 48: 22.4% versus 6.3%) and the spine (Week 24: 33.7% versus 8.0%; Week 48: 38.8% versus 4.4%).

Mean (SD) percentage changes from baseline were observed in hip BMD (Week 24: −0.022% [1.6853]; Week 48: −0.222% [2.3207]) and spine BMD (Week 24: −2.686 [4.5755]; Week 48: −4.538 [6.8917]) for Cohort 2 ART-naive subjects. Change from baseline for hip and spine BMD was < 3% in Cohort 2.

#### 2.1.9.2.2.3.1.3. Hip and Spine BMD Clinical Status

Overall, few Cohort 1 switch subjects or Cohort 2 ART-naive subjects had changes from baseline in hip and spine BMD clinical status.

2.1.9.2.2.3.2. Bone Laboratory Parameters

Overall, median percentage decreases from baseline for Cohort 1 switch subjects at Weeks 24 and 48 were observed in the bone biomarkers C telopeptide (bone resorption) and PINP (bone formation), as well as PTH, a hormone involved in bone metabolism. For each of the bone laboratory parameters, Cohort 1 switch subjects with pre-switch TDF use had median percentage decreases from baseline at Week 24, whereas those without pre-switch TDF use had median percentage increases from baseline at Week 24. Median (Q1, Q3; baseline value) percentage changes from baseline at Week 24 for subjects with and without pre-switch TDF use were as follows: C-telopeptide: with pre-switch TDF use −5.4% (−19.2%, 7.1%; 4.8 µg/L), without pre-switch TDF use 5.2% (−8.1%, 21.3%; 5.1 µg/L); PINP: with pre-switch TDF use −24.27% (−39.98%, 8.34%; 57.21 ng/mL), without pre-switch TDF use 8.94% (−15.64%, 43.64%; 45.43 ng/mL); PTH: with pre-switch TDF use −15.9% (−32.0%, 8.1%; 48.3 pg/mL), without pre-switch TDF use 14.6% (−9.3%, 65.2%; 43.4 pg/mL).

Overall, median percentage increases from baseline for Cohort 2 ART-naive subjects at Weeks 24 and 48 were observed in C-telopeptide, P1NP, and PTH.

2.1.9.2.2.4. ART-Naive Adolescent Subjects

2.1.9.2.2.4.1. Study GS-US-292-0106

Bone safety for Study GS-US-292-0106 is described in detail in the CSR (GS-US-292-0106 Interim CSR, Section 11.2.4.1).

2.1.9.2.2.4.1.1. Fracture Events

No fractures were reported in Study GS-US-292-0106.

2.1.9.2.2.4.1.2. Bone Mineral Density

**Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD**

Mean and median baseline values and percentage changes from baseline at Week 24 in spine and TBLH BMD are shown in Table 54.

**Table 54. E/C/F/TAF Study GS-US-292-0106: Baseline Value and Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD at Week 24 (Spine and TBLH DXA Analysis Sets)**

| | Spine (N = 23) | | TBLH (N = 23) | |
|---|---|---|---|---|
| **Time Point** | **Mean (SD)** | **Median (Q1, Q3)** | **Mean (SD)** | **Median (Q1, Q3)** |
| Baseline ($g/cm^2$) | 0.779 (0.2102) | 0.778 (0.677, 0.838) | 0.872 (0.1305) | 0.856 (0.805, 0.935) |
| % Change at Week 24 | 1.726 (4.2840) | 2.773 (−1.182, 4.557) | 0.772 (2.5631) | 0.340 (−1.228, 2.122) |

Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 36.1 and 36.2

Two of 23 subjects (8.7%) had a ≥ 4% decrease from baseline in spine BMD at the Week 24 assessment. One of these subjects had a height-age adjusted BMD Z-score > −2 at both baseline and Week 24; the other subject had a height-age adjusted BMD Z-score > −2 at baseline and ≤ 2 at Week 24. No subject had a ≥ 4% decrease from baseline in TBLH BMD at Week 24.

### Change from Baseline in Bone Mineral Density Z-Scores

BMD status was also assessed using BMD Z-scores. The Z-score for any BMD value is the number of SDs that value lies below or above the mean BMD of an age-, sex-, and race-matched control group. A Z-score ≤ –2.0 is "below the expected range for age" and is considered to reflect a low bone mass or BMD, while a Z-score > –2.0 is "within the expected range for age." In clinical terms, a Z-score ≤ –2.0 reflects a low bone mass or BMD {30329}. BMD Z-scores were also calculated adjusted for height-age. For both spine and TBLH, height-age adjusted mean and median Z-scores at baseline were closer to zero than unadjusted Z-scores, and changes from baseline in each at Week 24 were numerically smaller than for unadjusted Z-scores. Both spine and TBLH median (Q1, Q3) height-age adjusted BMD Z-scores were within the expected range for age.

Change from baseline in height-age adjusted spine BMD Z-score was as follows: mean (SD) −0.08 (0.391); median −0.02 (−0.15, 0.13). Change from baseline in height-age adjusted TBLH BMD Z-score was as follows: mean (SD) −0.10 (0.256); median −0.09 (−0.26, 0.10).

### Spine and Total-Body-Less-Head Clinical Status

Two subjects showed a worsening (change from > −2 to ≤ −2) in their spine or TBLH height-age adjusted BMD Z-scores from baseline at Week 24.

#### 2.1.9.2.3. RPV Studies

##### 2.1.9.2.3.1. ART Naive Subjects

###### 2.1.9.2.3.1.1. Studies C209 and C215

Dual Energy X-ray Absorptiometry scans were performed in substudies of the individual trials, C209 and C215, at baseline, Week 48, and Week 96 (or at the time of withdrawal from the main trial for subjects who discontinued the trial after 64 weeks of treatment), to compare the changes in body fat distribution and BMD on RPV 25 mg taken once daily vs control (EFV 600 mg taken once daily) in ARV treatment-naive HIV-1 infected subjects. In addition to comparing RPV with control, the effects of the background N(t)RTI regimen on limb fat, trunk fat, total body fat, bone mineral content, and BMD were explored. Analyses from pooled BMD data only are presented here.

A total of 413 HIV-1 infected, ARV treatment-naive adult subjects randomized in a 1:1 ratio in the main trial to receive either RPV 25 mg taken once daily (209 subjects) or control (204 subjects), were enrolled in the DEXA substudies (TMC278-TiDP6-C209/C215subDEXA).

Of the subjects included in the DEXA substudy pooling, 332 were male (169 subjects in the RPV group and 163 in the control group) and 81 were female (40 subjects in the RPV group and 41 in the control group). The majority of subjects were White (142 [67.9%] in the RPV group and 134 [65.7%] in the control group) (TMC278-C209-C215-DEXA-Display GEN.1).

Both treatment groups showed a small but statistically significant median decrease from baseline in BMD (1.4% and 1.5% in the RPV group and 1.4% and 1.5% in the control group at Week 48 and Week 96, respectively). No statistically significant differences were observed between treatment groups.

Statistical comparisons are presented in TMC278-C209-C215-DEXA-Display DEXA 2 to Display DEXA.6.

#### 2.1.9.3. Renal Safety

Renal parameters were assessed in all Phase 2 and 3 studies with E/C/F/TAF and Complera/Eviplera as renal toxicity has been associated with TDF use, and COBI inhibits tubular secretion of creatinine, leading to an increase in serum creatinine and a decrease in eGFR without an effect on aGFR.

Renal parameters were assessed in the Phase 2 and 3 studies with RPV and Complera/Eviplera as small increases in serum creatinine have been observed in humans treated with RPV, likely due to inhibition of renal transporters for creatinine. However, these are not considered to be clinically important {22839}.

#### 2.1.9.3.1. E/C/F/TAF Studies

#### 2.1.9.3.2. Methodology

In order to ensure a comprehensive assessment of renal safety, a thorough review was performed of all relevant data in the E/C/F/TAF studies for subjects with clinically significant AEs (SAEs and AEs leading to study drug discontinuation) in the renal and urinary disorders SOC and the renal function analyses HLT in the investigations SOC.

There is no commonly accepted laboratory definition of PRT to identify cases in which tubulopathy is likely to evolve clinically in a specific subject. STB clinical studies identified subjects with confirmed increases in serum creatinine plus confirmed increases in 2 of the 3 markers of tubular dysfunction for clinical review. In E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109, the same thresholds for creatinine and tubular dysfunction were used, but the sensitivity was increased, with subclinical renal tubulopathy defined as confirmed abnormalities in any 2 out of the 4 renal parameters (serum creatinine and 3 markers of tubular dysfunction) as follows:

- Increase in serum creatinine ≥ 0.40 mg/dL from baseline (≥ 0.24 mg/dL for the subjects in Study GS-US-292-0109 switching to E/C/F/TAF from therapies other than ATR). The serum creatinine cutoffs were based on the mean + 2 SD of the change in serum creatinine from baseline at Week 48 using pooled data from STB Phase 3 Studies GS-US-236-0102 and GS-US-236-0103. The cutoff of 0.40 mg/dL was based on results from the STB group, and the cutoff of 0.24 mg/dL was based on results from the ATR group.

- Confirmed ≥ 2 grade level increase from baseline in proteinuria

- Confirmed ≥ 1 grade level increase from baseline in hypophosphatemia

- Confirmed ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)

A confirmed laboratory abnormality was defined as an abnormality observed at 2 consecutive postbaseline measurements or an abnormality observed at 1 measurement followed by study drug discontinuation.

Given the known specificity of TFV nephrotoxicity at the proximal tubule cells, changes in tubular proteinuria were assessed by urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio, biomarkers specific for proteins secreted by the renal tubule.

##### 2.1.9.3.2.1. ART-Naive Subjects

###### 2.1.9.3.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Renal safety is described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 48 CSR, Section 11.2.4.2; GS-US-292-0111 Week 48 CSR, Section 11.2.4.2).

#### 2.1.9.3.2.1.1.1. Renal Events

Two subjects in Study GS-US-292-0104, 1 in each treatment group, had a renal SAE, neither of which resulted in discontinuation of study drugs nor was considered related to study drugs by the investigator: Grade 2 nephrotic syndrome (E/C/F/TAF) and Grade 2 acute renal failure (reported as acute kidney injury; STB). In Study GS-US-292-0111, 1 renal SAE (ureteric calculus) was reported for 1 subject in the E/C/F/TAF group, and the event was not considered related to study drugs by the investigator.

Three subjects in Study GS-US-292-0104, all in the STB group, had renal AEs that resulted in discontinuation of study drugs (nephropathy, renal failure, and decreased GFR); the events were nonserious and considered related to study drugs by the investigator. One subject in the STB group in Study GS-US-292-0111 had a renal AE that resulted in discontinuation of study drugs: nonserious, Grade 3 renal failure (reported as renal insufficiency) with concurrent AEs of hypertensive crises and cerebrovascular accident. The renal failure was considered related to study drugs by the investigator.

There were no subjects who reported proximal tubulopathy (including Fanconi syndrome) (E/C/F/TAF ISS, Table 7).

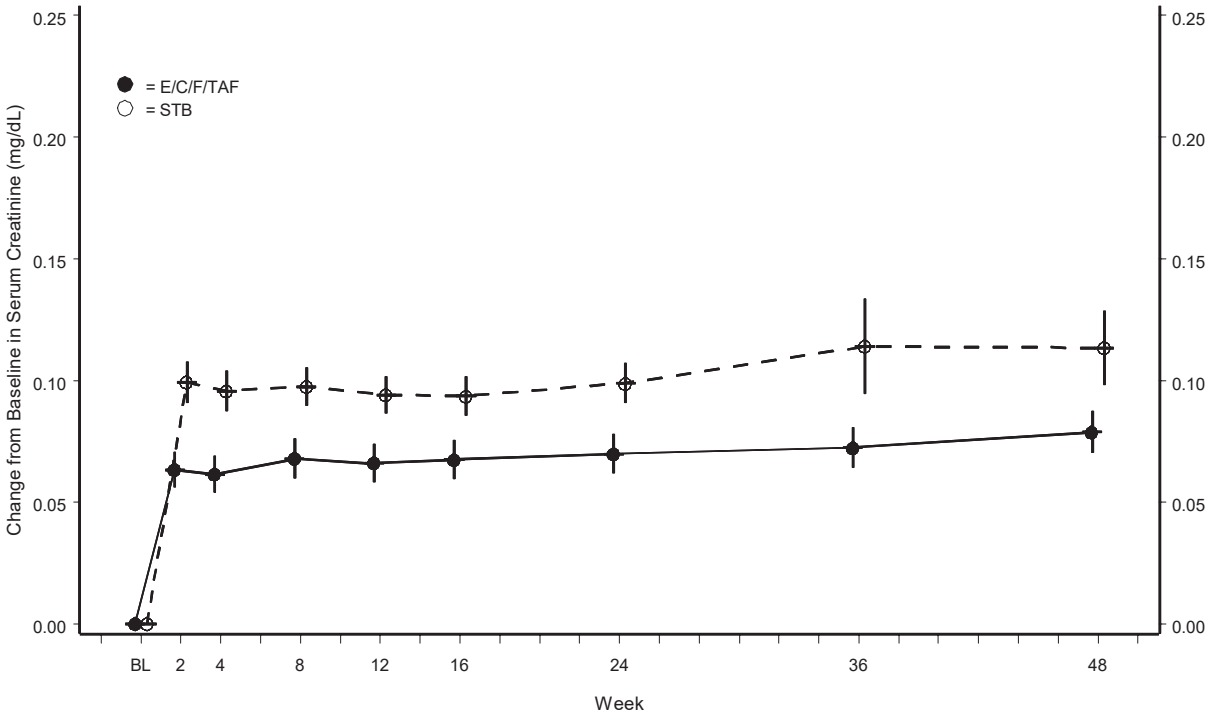
#### 2.1.9.3.2.1.1.2. Renal Laboratory Parameters

**Serum Creatinine**

The change from baseline in serum creatinine at Week 48 was the third alpha-protected key safety endpoint for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111. Statistical analysis using the fallback procedure confirmed significance using an adjusted alpha, which was dependent on the results from preceding tests. Overall, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group (Figure 11). Mean (SD) baseline serum creatinine values were as follows: E/C/F/TAF 0.93 (0.172) mg/dL, STB 0.94 (0.169) mg/dL (E/C/F/TAF ISS, Table 26.2). Increases were observed by Week 2 for each treatment group, and remained stable through Week 48. Mean (SD) changes from baseline were as follows: Week 2, E/C/F/TAF 0.06 (0.105) mg/dL, STB 0.10 (0.121) mg/dL ($p < 0.001$); Week 48, E/C/F/TAF 0.08 (0.124) mg/dL, STB 0.11 (0.217) mg/dL ($p < 0.001$). The difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48.

Analysis using LOCF to replace missing values showed similar results to the observed data (E/C/F/TAF ISS, Table 26.1).

**Figure 11. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data; Safety Analysis Set)**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 866 | 826 | 856 | 847 | 843 | 845 | 836 | 830 | 820 |
| STB (n=): | 867 | 844 | 858 | 852 | 841 | 843 | 834 | 816 | 806 |

BL = Baseline.

Data Extracted: s292-0104: CRF,DXA Data: 03SEP2014, Lab Data: 04SEP2014, s292-0111: CRF,DXA Data: 22SEP2014, Lab Data: 23SEP2014
Source: .../version1/prog/t-lab-creat.sas v9.2 Output file: g-labc-creat-mn.out 26SEP2014:17:45

Source: E/C/F/TAF ISS, Figure 5.2

Graded laboratory abnormalities for serum creatinine were reported for 3.7% of subjects (n = 32) in the E/C/F/TAF group and 5.0% of subjects (n = 43) in the STB group (E/C/F/TAF ISS, Table 18). Most of these abnormalities were Grade 1. Grade 2 serum creatinine abnormalities were reported for 1 subject in the E/C/F/TAF group and 4 subjects in the STB group. Two subjects, both in the STB group, had a Grade 4 serum creatinine abnormality.

### Estimated Glomerular Filtration Rate

Overall, decreases from baseline in median $eGFR_{CG}$ values were smaller in the E/C/F/TAF group compared with the STB group (Table 55 and Figure 12). Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: E/C/F/TAF 117.0 (99.6, 135.6) mL/min, STB 113.9 (99.0, 133.6) mL/min. Decreases were observed by Week 2 for each treatment group and remained stable through Week 48. Median (Q1, Q3) changes from baseline were as follows: Week 2, E/C/F/TAF −7.2 (−15.0, 0.5) mL/min, STB −10.2 (−17.9, −3.1) mL/min ($p < 0.001$); Week 48, E/C/F/TAF −6.4 (−15.4, 2.4) mL/min, STB −11.2 (−20.2, −2.3) mL/min ($p < 0.001$). The

difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48.

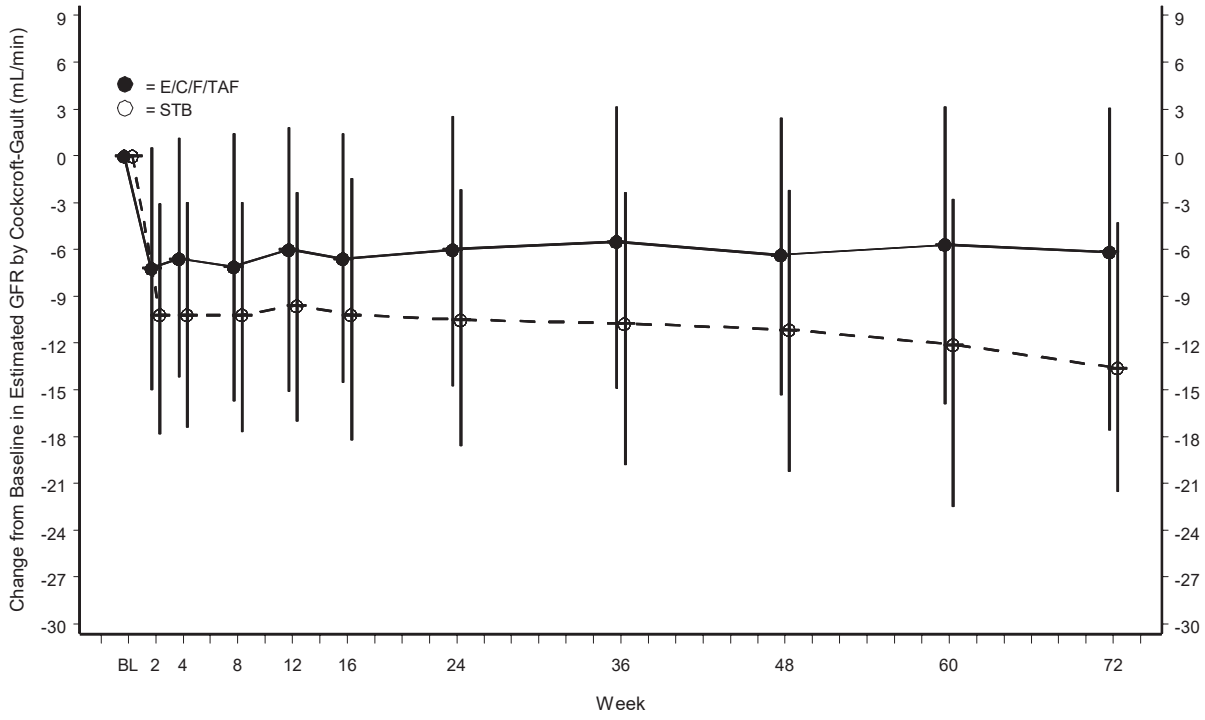
Observations for changes from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ support those seen for $eGFR_{CG}$ (E/C/F/TAF ISS, Table 27.2).

**Table 55. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Changes from Baseline in $eGFR_{CG}$ at Weeks 24 and 48 (Safety Analysis Set)**

| | E/C/F/TAF (N=866) | STB (N=867) | p-value |
|---|---|---|---|
| Baseline | | | |
| N | 866 | 867 | 0.082 |
| Mean (SD) | 120.8 (30.87) | 118.7 (30.73) | |
| Median | 117.0 | 113.9 | |
| Q1, Q3 | 99.6, 135.6 | 99.0, 133.6 | |
| Change at Week 24 | | | |
| N | 836 | 833 | <0.001 |
| Mean (SD) | −6.3 (14.63) | −10.2 (14.28) | |
| Median | −6.0 | −10.5 | |
| Q1, Q3 | −14.8, 2.5 | −18.6, −2.2 | |
| Change at Week 48 | | | |
| N | 820 | 804 | <0.001 |
| Mean (SD) | −6.6 (15.37) | −11.2 (15.01) | |
| Median | −6.4 | −11.2 | |
| Q1, Q3 | −15.4, 2.4 | −20.2, −2.3 | |

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: E/C/F/TAF ISS, Table 27.1

**Figure 12. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) Change from Baseline in $eGFR_{CG}$ (mL/min) by Visit (Safety Analysis Set)**




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 866 | 825 | 854 | 847 | 842 | 845 | 836 | 829 | 820 | 396 | 128 |
| STB (n=): | 867 | 844 | 858 | 850 | 841 | 843 | 833 | 814 | 804 | 375 | 117 |

BL = Baseline.

Data Extracted: s292-0104: CRF,DXA Data: 03SEP2014, Lab Data: 04SEP2014, s292-0111: CRF,DXA Data: 22SEP2014, Lab Data: 23SEP2014
Source: .../version1/prog/t-lab.sas v9.2 Output file: g-labc-creatclr.out 26SEP2014:17:46

Source: E/C/F/TAF ISS, Figure 6.1

## Proteinuria by Urinalysis (Dipstick)

Proteinuria by urinalysis (dipstick) through Week 48 data cut was the fourth key alpha-protected safety endpoint for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111. Fewer subjects in the E/C/F/TAF group than in the STB group had at least 1 recorded, graded proteinuria by dipstick during the study (E/C/F/TAF 31.2% [269 of 862 subjects]; STB 36.8% [318 of 865 subjects]; p = 0.022; E/C/F/TAF ISS, Table 28). Of the subjects who had proteinuria by urinalysis, most were Grade 1.

Eight subjects (0.9%) in the E/C/F/TAF group and 14 subjects (1.6%) in the STB group had AEs of proteinuria; in addition, 1 subject in the E/C/F/TAF group and 2 subjects in the STB group had an AE of protein urine present (E/C/F/TAF ISS, Table 7). Three subjects (E/C/F/TAF 2 subjects, STB 1 subject) had AEs of proteinuria assessed by the investigator as Grade 2; all other AEs of proteinuria were Grade 1. The AEs of proteinuria were considered related to study

drugs by the investigator for 7 subjects in the E/C/F/TAF group and 10 subjects in the STB group (E/C/F/TAF ISS, Table 11).

**Proteinuria by Quantitative Assessment**

There was a decrease from baseline in median UPCR for the E/C/F/TAF group that was observed at Week 2 and persisted through Week 48. In contrast, there was an increase from baseline in UPCR in the STB group (median [Q1, Q3] percentage change from baseline at Week 48: E/C/F/TAF: −3.4% [−34.5%, 42.6%]; STB: 19.8% [−23.0%, 75.8%]; Table 56). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

There was a decrease from baseline in median UACR for the E/C/F/TAF group at Week 48 compared with an increase in the STB group (median [Q1, Q3] percentage change from baseline at Week 48: E/C/F/TAF −4.7% [−32.9%, 35.6%]; STB 7.1% [−26.5%, 62.1%]; $p = 0.001$; Table 56).

A summary of UACR to UPCR ratios from baseline to Week 48 in Study GS-US-292-0104 showed no change in the median percentage change from baseline for the E/C/F/TAF group compared with a decrease for the STB group at Week 48; the difference was statistically significant between treatment groups at Week 48 ($p = 0.022$). In Study GS-US-292-0111, there were no differences in UACR to UPCR ratio between treatment groups at Week 48. In both studies, urine creatinine was similar for both treatment groups at each measured time point.

**Table 56. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Renal Biomarkers at Week 48**

| Parameter | Median Percentage Change (%) (Q1, Q3) | | p-value[a] |
|---|---|---|---|
| | E/C/F/TAF | STB | |
| UPCR (mg/g) | −3.4% (−34.5%, 42.6%) | 19.8% (−23.0%, 75.8%) | <0.001 |
| UACR (mg/g) | −4.7% (−32.9%, 35.6%) | 7.1% (−26.5%, 62.1%) | 0.001 |
| RBP to Urine Creatinine Ratio (µg/g) | 9.2% (–23.0%, 48.6%) | 51.2% (2.9%, 132.9%) | <0.001 |
| Beta-2-microglobulin to Urine Creatinine Ratio (µg/g) | −31.7% (–57.3%, 3.7%) | 24.1% (–33.8%, 167.9%) | <0.001 |

a p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: E/C/F/TAF ISS, Tables 29.1 to 29.4

**Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio**

There was an initial decrease from baseline in RBP to creatinine ratio, followed by a small increase after Week 12 for the E/C/F/TAF group, and a progressive increase from baseline to Week 48 for the STB group (median percentage change from baseline at Week 48: E/C/F/TAF

9.2% [−23.0%, 48.6%]; STB 51.2% [2.9%, 132.9%]; Table 56). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

The median percentage change from baseline in beta-2-microglobulin to creatinine ratio decreased for the E/C/F/TAF group and increased for the STB group through Week 48 (median percentage change from baseline at Week 48: E/C/F/TAF −31.7% [–57.3%, 3.7%], STB 24.1% [−33.8%, 167.9%]; Table 56). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

**Other Renal Biomarkers**

Other renal biomarkers included the marker of proximal renal tubular function, FEUA, and measures of renal phosphate handling, TmP/GFR, and $FEPO_4$, each using unadjusted and adjusted serum creatinine values.

There was no change from baseline in median (Q1, Q3) FEUA using adjusted serum creatinine at Week 48 in the E/C/F/TAF group, compared with an increase in the STB group (E/C/F/TAF 0.0% [–1.3%, 1.1%]; STB 0.4% [–0.8%, 2.0%]; E/C/F/TAF ISS, Table 33.2). The difference between treatment groups was statistically significant at all time points ($p < 0.001$ at Week 48).

At Week 48, there were no differences in median (Q1, Q3) TmP/GFR between treatment groups (E/C/F/TAF −0.1% [−0.6%, 0.4%]; STB −0.2% [−0.6%, 0.3%]; $p = 0.18$; E/C/F/TAF ISS, Table 31.2).

Median (Q1, Q3) $FEPO_4$ using adjusted serum creatinine was increased relative to baseline through Week 48 for both groups (E/C/F/TAF 0.9% [–2.0%, 4.5%]; STB 1.7% [–1.6%, 5.3%]; E/C/F/TAF ISS, Table 32.2). The increase was significantly greater in the STB group relative to the E/C/F/TAF group ($p = 0.005$ at Week 48).

Similar results for FEUA, TmP/GFR, and $FEPO_4$ were observed when values were calculated using unadjusted serum creatinine (E/C/F/TAF ISS, Tables 31.1, 32.1, and 33.1).

**Markers of Subclinical Proximal Renal Tubulopathy**

No subjects in the E/C/F/TAF group met the criteria for PRT.

2.1.9.3.2.1.2. Study GS-US-292-0102

Renal safety for Study GS-US-292-0102 is described in detail in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.2.4.2).

2.1.9.3.2.1.2.1. Renal Events

In the randomized phase, no subjects discontinued study drugs due to a renal AE.

Two subjects in the E/C/F/TAF group had events of renal failure, considered unrelated to study drugs by the investigator. Neither event resulted in discontinuation of study drugs. No cases of renal failure were reported for subjects in the STB group. Subject [redacted] in the E/C/F/TAF

group had a Grade 1, nonserious AE of renal failure (reported as renal insufficiency; maximum serum creatinine 1.5 mg/dL) related to volume depletion and the SAE of pyelonephritis. The event resolved within 2 days of onset. Subject [redacted] in the E/C/F/TAF group had an SAE of acute renal failure due to volume depletion during the extension phase. Renal function returned to normal and treatment with the study drugs, which was interrupted for 6 days, was resumed.

There were no cases of PRT reported (including Fanconi syndrome) in either treatment group.

2.1.9.3.2.1.2.2. Renal Laboratory Parameters

**Serum Creatinine**

In the randomized phase, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. Increases were observed at Week 2 for each treatment group and remained stable through Week 48. Mean (SD) increases from baseline at Week 48 were as follows: E/C/F/TAF 0.08 (0.112) mg/dL, STB 0.12 (0.144) mg/dL (p = 0.011). No graded abnormalities of serum creatinine were reported.

Analysis using LOCF to replace missing values showed similar results to the observed data for the randomized phase.

In the E/C/F/TAF group at Week 96, increases from baseline in mean values for serum creatinine were consistent with results at Week 48.

**Estimated Glomerular Filtration Rate**

In the randomized phase, decreases from baseline in median $eGFR_{CG}$ were smaller in the E/C/F/TAF group compared with the STB group. Decreases were observed at Week 2 for each treatment group and remained stable through Week 48. Median decreases from baseline at Week 48 were as follows: E/C/F/TAF 5.5 mL/min, STB 10.1 mL/min; p = 0.041.

Observations for changes from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ and $eGFR_{CKD\text{-}EPI,\ cysC}$ support those seen for $eGFR_{CG}$.

In the E/C/F/TAF group at Week 96, changes from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ were consistent with results at Week 48.

**Proteinuria by Urinalysis (Dipstick)**

In the randomized phase, proteinuria was reported for 26.1% of subjects (n = 29) in the E/C/F/TAF group and 34.5% of subjects (n = 20) in the STB group. Most proteinuria by dipstick was Grade 1 (E/C/F/TAF 23 subjects; STB 19 subjects). One subject in the E/C/F/TAF group had a laboratory abnormality of Grade 3 proteinuria that was also reported as a Grade 1, nonserious AE. The event was not considered related to study drugs by the investigator, and did not result in discontinuation of treatment with study drugs. The subject had negative proteinuria at baseline, which increased to Grade 1 at Week 8, was negative at Weeks 12 and 16, and was

Grade 3 at Week 24. Values fluctuated between negative, trace and 1+ until Week 62, and then remained negative through Week 96. There were no clinically relevant changes in serum creatinine or eGFR after Week 4; quantitative urine protein declined through Week 96; and there was no laboratory or clinical evidence of renal dysfunction.

**Proteinuria by Quantitative Assessment**

In the randomized phase, no statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR (at Week 48, median percentage changes from baseline for UPCR: E/C/F/TAF −7.2%, STB 13.5%; p = 0.092, for UACR: E/C/F/TAF −6.9%, STB 8.1%; p = 0.089).

In the E/C/F/TAF group at Week 96, median percentage changes from baseline in UPCR and UACR were consistent with results at Week 48.

**Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio**

In the randomized phase, there was no change from baseline at Week 48 in RBP to creatinine ratio for the E/C/F/TAF group; however, an increase from baseline was seen for the STB group (E/C/F/TAF −0.1%, STB 36.2%; p = 0.002 for the difference between groups). The median percentage change from baseline in beta-2-microglobulin to creatinine ratio decreased for the E/C/F/TAF group compared with no change for the STB group through Week 48 (change from baseline at Week 48: E/C/F/TAF −40%, STB −1%; p = 0.007 for the difference between groups).

At Week 96, there was a transient increase in median RBP to creatinine ratio for the E/C/F/TAF group (change from baseline at Week 96 was 20.6%). The median decrease from baseline in beta-2-microglobulin to creatinine ratio at Week 96 was consistent with that at Week 48.

**Other Renal Biomarkers**

There were no changes from baseline in median values for the other renal biomarkers in either group during the randomized phase, with no statistically significant differences between the 2 groups.

There were no changes from baseline at Week 96 in median values for the other renal biomarkers for the E/C/F/TAF group.

2.1.9.3.2.2. Virologically Suppressed Subjects in E/C/F/TAF Studies

2.1.9.3.2.2.1. Study GS-US-292-0109

Renal safety for Study GS-US-292-0109 is described in detail in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.2.4.2).

#### 2.1.9.3.2.2.1.1. Renal Events

One subject in the FTC/TDF+3rd Agent group had a study drug-related SAE of acute renal failure that did not result in discontinuation of study drug. In the E/C/F/TAF group, 2 subjects had nonserious renal AEs (tubulointerstitial nephritis [subject had recurrent hematuria on and off treatment and was diagnosed with Hodgkin's disease after treatment discontinuation] and acute renal failure [event was prerenal, linked to Hodgkin's disease and generalized worsening]) that resulted in discontinuation of the study drug; both events were considered by the investigator as not related to study drug.

There were no AEs of PRT (including Fanconi Syndrome) reported in the E/C/F/TAF group. One subject in the FTC/TDF+3rd Agent group (taking ATV+COBI+TVD) had a study drug-related, nonserious AE of acquired Fanconi syndrome that resulted in discontinuation of study drug.

#### 2.1.9.3.2.2.1.2. Renal Laboratory Parameters

**Serum Creatinine**

There were decreases or no changes from baseline in mean serum creatinine values in the E/C/F/TAF group as compared with increases or no changes from baseline in the FTC/TDF+3rd Agent group after excluding subjects switching from ATR ($p \leq 0.014$ for the differences between treatment groups at Weeks 2 through 48). At Week 48, the mean (SD) changes from baseline in serum creatinine were as follows: E/C/F/TAF −0.01 (0.117) mg/dL; FTC/TDF+3rd Agent 0.04 (0.123) mg/dL ($p < 0.001$ for the difference between groups).

For changes in serum creatinine analyzed by prior treatment regimen, decreases from baseline were observed among subjects who switched to E/C/F/TAF from STB, and either increases or no changes from baseline at most time points among the subjects who switched to E/C/F/TAF from ATV/boosted regimens. In contrast, among subjects who switched to E/C/F/TAF from ATR, increases in serum creatinine were observed at Week 2 (consistent with the established COBI effect on serum creatinine), and through Week 48.

**Estimated Glomerular Filtration Rate**

There were increases from baseline in $eGFR_{CG}$ values in the E/C/F/TAF group compared with decreases from baseline in the FTC/TDF+3rd Agent group at Weeks 2 through 48 after excluding subjects switching from ATR. Median changes from baseline at Week 48 were: E/C/F/TAF 1.8 mL/min, FTC/TDF+3rd Agent −3.7 mL/min ($p < 0.001$ for the difference between groups). The changes from baseline in $eGFR_{CG}$ corresponded with those observed for serum creatinine at most time points in both treatment groups among subjects with STB or ATR as their prior regimen and among subjects who remained on ATV/boosted+TVD regimens. Among subjects who switched to E/C/F/TAF from ATV/boosted+TVD regimens, increases from baseline in $eGFR_{CG}$ were observed at most time points, and there was generally no correspondence between $eGFR_{CG}$ and serum creatinine values.

**Proteinuria by Urinalysis (Dipstick)**

Based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had improvements from baseline in proteinuria (E/C/F/TAF 7.1%, 55 of 772 subjects; FTC/TDF+3rd Agent 5.6%, 21 of 374 subjects) and a lower percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening proteinuria (E/C/F/TAF 4.3%, 33 of 772 subjects; FTC/TDF+3rd Agent 7.0%, 26 of 374 subjects).

Proteinuria was reported as an AE for a similar percentage of subjects in each treatment group (E/C/F/TAF 1.4%; FTC/TDF+3rd Agent 1.3%); all AEs of proteinuria were Grade 1 or 2 in severity and none resulted in discontinuation of study drugs.

**Proteinuria by Quantitative Assessment**

There were decreases from baseline in UPCR and UACR in the E/C/F/TAF group as compared with increases from baseline in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows:

- UPCR: E/C/F/TAF −18.5% (−45.5, 18.1); FTC/TDF+3rd Agent 9.4% (−16.9, 51.8)
- UACR: E/C/F/TAF −18.4% (−45.1, 21.0); FTC/TDF+3rd Agent 5.3% (−25.5, 58.5)

Decreases from baseline in UPCR and UACR were observed in the E/C/F/TAF group regardless of prior treatment regimen.

**Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio**

There were decreases from baseline in the E/C/F/TAF group in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios compared with increases from baseline in both parameters at most time points in the FTC/TDF+3rd Agent group ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline at Week48).

Median (Q1, Q3) percentage changes from baseline in RBP to creatinine and beta-2-microglobulin to creatinine ratios at Week 48 were as follows:

- RBP to creatinine ratio: E/C/F/TAF −32.9% (−63.9, 0.0); FTC/TDF+3rd Agent 15.7% (−22.9, 75.1)
- Beta-2-microglobulin to creatinine ratio: E/C/F/TAF −49.2% (−80.0, −4.9); FTC/TDF+3rd Agent 14.4% (−33.6, 92.9)

Decreases from baseline in both the RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed in the E/C/F/TAF group regardless of prior treatment regimen ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline at Week48).

**Other Renal Biomarkers**

The magnitude of the decrease from baseline in TmP/GFR at Week 48 was comparable in both treatment groups, excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF −0.1 mg/dL, FTC/TDF+3rd Agent −0.1 mg/dL; p = 0.63). There was minimal change from baseline in $FEPO_4$ at Week 48 in the E/C/F/TAF compared with an increase from baseline the FTC/TDF+3rd Agent group, excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF 0.1%, FTC/TDF+3rd Agent 0.7%; p = 0.023).

There was a decrease from baseline in FEUA at Week 48 in the E/C/F/TAF group compared with minimal change from baseline in the FTC/TDF+3rd Agent group, excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF −0.8%, FTC/TDF+3rd Agent 0.1%; p < 0.001). A decrease from baseline in FEUA was observed in the E/C/F/TAF group regardless of prior treatment regimen.

**Markers of Subclinical Renal Tubulopathy**

No subjects in the E/C/F/TAF group had laboratory findings consistent with subclinical renal tubulopathy. One subject ([redacted]) in the FTC/TDF+3rd Agent (taking ATV+COBI+TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

2.1.9.3.2.2.2. Study GS-US-292-0102 Open-Label Extension

2.1.9.3.2.2.2.1. Renal Events

There were no cases of renal failure, and no subjects discontinued study drug due to renal AEs in the switch groups during the extension phase of Study GS-US-292-0102.

There were no cases of PRT (including Fanconi Syndrome).

2.1.9.3.2.2.2.2. Renal Laboratory Parameters

**Serum Creatinine**

In the all TDF to TAF group, decreases from baseline in mean values for serum creatinine were observed as early as Week 2 of the extension phase and were maintained through Week 24 (the mean baseline value was 1.12 mg/dL; mean changes from baseline by visit at Weeks 2 through 24 ranged from −0.02 to −0.05 mg/dL). In the D/C/F/TAF to E/C/F/TAF group, a decrease from baseline in serum creatinine was observed at Week 24 of the extension phase (−0.03 mg/ dL).

**Estimated Glomerular Filtration Rate**

In the all TDF to TAF group, increases from baseline in median values for $eGFR_{CG}$ were observed at as early as Week 2 of the extension phase and were maintained through Week 24: the median baseline value was 99.0 mL/min; the median changes from baseline by visit at

Weeks 2 through 24 ranged from 3.2 to 5.8 mL/min. In the D/C/F/TAF to E/C/F/TAF group, the median changes from baseline in $eGFR_{CG}$ from Week 4 through Week 24 by visit ranged from 0.4 to 3.8 mL/min.

**Proteinuria by Urinalysis (Dipstick)**

All urine protein abnormalities reported in the switch groups were Grade 1 or Grade 2, and none were reported as an AE.

**Proteinuria by Quantitative Assessment**

In the all TDF to TAF group, decreases from baseline in UPCR and UACR were seen at Week 24; the median percentage change from baseline at Week 24 for UPCR was −13.0% and for UACR was −10.3%. In the D/C/F/TAF to E/C/F/TAF group, there were no consistent changes from baseline in median values for these parameters.

**Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio**

In the all TDF to TAF group, the median percentage change from baseline at Week 24 for the RBP to creatinine ratio was −12.5% and for the beta-2-microglobulin to creatinine ratio was −32.0%. In the D/C/F/TAF to E/C/F/TAF group, the median percentage change from baseline at Week 24 for the RBP to creatinine ratio was −2.5% and for the beta-2-microglobulin to creatinine ratio was −12.0%.

**Other Renal Biomarkers**

In the switch groups, there were no changes from baseline in median values for the other renal biomarkers.

**Markers of Subclinical Proximal Renal Tubulopathy**

There were no laboratory findings consistent with subclinical renal tubulopathy.

2.1.9.3.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.9.3.2.3.1. Study GS-US-292-0112

Renal safety for Study GS-US-292-0112 is described in detail in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.2).

2.1.9.3.2.3.1.1. Renal Events

One subject (0.4%) in Cohort 1 had an SAE in the renal and urinary disorders SOC. Subject [redacted] (baseline $eGFR_{CG} \geq 50$ mL/min group) had a single Grade 3 serum creatinine elevation concurrent with an SAE of acute renal failure; the event was considered unrelated to study drug by the investigator and did not result in discontinuation of study drug. The SAE of

acute renal failure resolved 2 days after onset and the subject's serum creatinine values decreased to below the baseline value (1.85 mg/dL) at each subsequent visit.

Two of 242 subjects (0.8%) in Cohort 1 (both in the baseline $eGFR_{CG}$ < 50 mL/min group) had an AE in the renal and urinary disorders SOC that led to study drug discontinuation (renal failure and renal failure chronic). Both discontinuations were due to declining GFR, 1 subject had labile hypertension and was using concomitant ramipril and valsartan, and the discontinuation for another subject was assessed as likely related to progression of CKD and not related to study drug.

No renal SAEs or AEs in the renal and urinary disorders SOC that led to study drug discontinuation were reported for Cohort 2 ART-naive subjects.

There were no AEs of proximal tubulopathy (including Fanconi Syndrome).

2.1.9.3.2.3.1.2. Renal Laboratory Parameters

**Actual GFR**

The aGFR was directly measured at baseline, Week 2, 4, and/or 8, and Week 24 using $CL_{iohexol}$ for subjects enrolled in the PK/PD substudy (N = 32). Median (Q1, Q3) changes from baseline in aGFR were −1.8 (−5.3, 3.7) mL/min at Week 2, 4, or 8 and 0.1 (−4.3, 4.4) at Week 24. The GLSM ratios (90% CIs) for Week 2, 4, or 8 and Week 24 versus baseline were 98.94 (93.71, 104.46) and 102.66 (97.11, 108.53), respectively, indicating aGFR was not affected by E/C/F/TAF over 24 weeks of treatment. There was no mean change in aGFR between subjects with baseline $eGFR_{CG}$ < 50 mL/min compared with subjects with baseline $eGFR_{CG} \geq 50$ mL/min. There was also no change in aGFR between subjects with or without pre-switch TDF use. The 90% CIs of the GLSM ratios in all cases were within 80% to 125%.

**Serum Creatinine, Cystatin C, and Phosphorus**

Median changes from baseline at each time point through Week 48 ranged from −0.01 to 0.04 mg/dL for serum creatinine, −0.06 to −0.01 mg/dL for serum cystatin C, and 0 to 0.3 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters. In subjects whose last prior ART regimen did not include TDF (N = 84), mean (SD) change from baseline in serum creatinine at Week 24 was 0.05 (0.280) mg/dL (E/C/F/TAF ISS, Table Req6909.4).

In Cohort 2 (ART-naive) subjects, median changes from baseline in serum creatinine at each time point through Week 48 ranged from −0.01 to 0.13 mg/dL, indicating no clinically significant changes in serum creatinine in these subjects. Graded serum creatinine laboratory abnormalities (Grade 1 only) were reported for 1 subject. Median changes from baseline at each time point through Week 48 ranged from −0.13 to 0.19 mg/dL for serum cystatin C and −0.6 to 0.2 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters.

**Estimated Glomerular Filtration Rate**

The primary renal endpoints for Study GS-US-292-0112 were defined as change from baseline at Week 24 in $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ cysC}$, and $eGFR_{CKD\text{-}EPI,\ creatinine}$. No clinically significant changes from baseline eGFR through Week 24 were observed using any of the 3 equations in the Cohort 1 switch and Cohort 2 ART-naive subjects.

In Cohort 1 (switch), the overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at Week 24 was −0.4 (−4.7, 4.5) mL/min for $eGFR_{CG}$, −1.8 (−6.1, 4.9) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.8 (−4.8, 11.2) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ cysC}$. The baseline $eGFR_{CG}$ < 50 mL/min group had median increases from baseline at Weeks 24 and 48 using any of the 3 equations. The baseline $eGFR_{CG} \geq 50$ mL/min group had an increase in eGFR as assessed by $eGFR_{CKD\text{-}EPI,\ cysC}$ and decreases as assessed by $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at Weeks 24 and 48.

In Cohort 2 (ART-naive), the median (Q1, Q3) change from baseline in eGFR at Week 24 (primary endpoint) was −0.3 (−3.6, 1.3) mL/min for $eGFR_{CG}$, −2.6 (−11.1, −0.9) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.9 (−3.3, 13.2) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ cysC}$.

**Proteinuria by Urinalysis (Dipstick)**

Most subjects in Cohort 1 had either no change or an improvement (toxicity grade decreased at least 1 grade from baseline) from the baseline proteinuria toxicity grade at Week 24. For 75.0% of subjects (57 of 76) with nonmissing values, the proteinuria grade improved from baseline at Week 24, of whom 22 of 33 (66.7%) had baseline $eGFR_{CG} < 50$ mL/min and 35 of 43 (81.4%) had baseline $eGFR_{CG} \geq 50$ mL/min. For only 5.7% of subjects (13 of 230) with nonmissing values, proteinuria grade worsened from baseline at Week 24, of whom 9 of 75 (12.0%) had baseline $eGFR_{CG} < 50$ mL/min and 4 of 155 (2.6%) had baseline $eGFR_{CG} \geq 50$ mL/min. At Week 24, most subjects had either no change or an improvement (decrease) from the baseline proteinuria toxicity grade irrespective of pre-switch TDF use. In subjects whose last prior antiretroviral regimen did not include TDF, 53% of subjects had an improvement (ie, decrease at least 1 toxicity grade) from baseline in proteinuria as measured by urine dipstick at Week 24 (E/C/F/TAF ISS, Table Req6756.16).

No changes from the baseline proteinuria toxicity grade were observed for Cohort 2 ART-naive subjects.

**Proteinuria by Quantitative Assessment**

In Cohort 1 (switch subjects), decreases in UPCR from the baseline median of 160.6 mg/g were observed at Week 1 (median of 110.3 mg/g) and persisted through Week 48 (median of 80.1 mg/g). Median (Q1, Q3) UPCR percentage change from baseline at Week 24 was −35.3% (−62.3%, 9.4%). For subjects with baseline $eGFR_{CG} < 50$ mL/min, median (Q1, Q3) baseline UPCR was 270.0 (105.5, 499.5) mg/g, and median (Q1, Q3) percentage change from baseline at Week 24 was −27.6% (−64.8%, 12.2%); for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median (Q1, Q3) baseline UPCR was 138.5 (68.4, 269.3) mg/g, and median (Q1, Q3) percentage change from baseline format Week 24 was −38.5% (−62.3%, 8.9%). Similar to UPCR, decreases

in UACR from the baseline median (Q1, Q3) of 28.8 (7.9, 83.9) mg/g were observed at Week 1 (median of 16.6 mg/g) and persisted through Week 48 (median of 8.3 mg/g). Median (Q1, Q3) UACR percentage changes from baseline at Week 24 was −38.8% (−72.7%, −0.8%). For subjects with baseline $eGFR_{CG}$ < 50 mL/min, median (Q1, Q3) baseline UACR was 53.2 (14.6, 240.8) mg/g, and median (Q1, Q3) percentage change from baseline at Week 24 was −28.6% (−69.9%, 10.2%). For subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median (Q1, Q3) baseline UACR was 22.7 (6.0, 60.6) mg/g, and median (Q1, Q3) percentage changes from baseline at Week 24 was −43.6% (−73.8%, −6.0%).

Clinically significant proteinuria (UPCR > 200 mg/g) was reported for 42.2% of subjects (101 of 239) with nonmissing values at baseline and 21.2% of subjects (48 of 226) with nonmissing values at Week 24. Clinically significant albuminuria (UACR ≥ 30 mg/g) was reported for 48.9% of subjects (115 of 235) with nonmissing values at baseline and 27.0% of subjects (62 of 230) with nonmissing values at Week 24. In subjects whose last prior antiretroviral regimen did not include TDF, median percentage change from baseline at Week 24 was 0.1% and −19.5%, respectively, for UPCR and UACR (E/C/F/TAF ISS, Tables Req6909.8 and Req6909.9).

In Cohort 2 (ART-naive subjects), changes from baseline in median UPCR and UACR were observed, but no subject developed new clinically significant proteinuria (UPCR > 200 mg/g) or clinically significant albuminuria (UACR ≥ 30 mg/g). Changes in UPCR from the baseline median of 45.9 mg/g were observed from Weeks 1 to 48, with medians of 50.8, 48.8, 48.7, 48.4, 55.0, 43.2, 58.2, 48.9, and 59.9 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively. Changes in UACR from the baseline median of 12.3 mg/g were observed from Weeks 1 to 48, with medians of 5.3, 7.8, 10.4, 8.1, 8.9, 7.2, 12.4, 7.1, and 8.6 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively.

**Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio**

Decreases in median percentage change from baseline in urine RBP to creatinine ratio (baseline of 800.5 µg/g) and beta-2-microglobulin to creatinine ratio (baseline of 1562.5 µg/g) were observed from Weeks 1 to 48: RBP to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −71.9% to −43.4%; beta-2-microglobulin to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −80.5% to −48.2%. In subjects whose last prior antiretroviral regimen did not include TDF, median percentage change from baseline at Week 24 was −5.5% and −11.8%, respectively, for RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio (E/C/F/TAF ISS, Tables Req6909.6 and Req6909.7).

Changes in urine RBP to creatinine ratio were observed from Weeks 1 to 48 for Cohort 2 ART-naive subjects, with median percentage changes from baseline of 12.1%, −20.8%, −5.0%, −9.6%, 68.8%, and 69.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively. Changes in beta-2-microglobulin to creatinine ratio were observed from Weeks 1 to 48, with median percentage changes from baseline of −15.2%, 43.4%, −47.1%, −10.2%, −19.5%, and 34.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively.

**Other Renal Biomarkers**

Other renal biomarkers included TmP/GFR ratio, $FEPO_4$, urine FEUA, and urine creatinine. In Cohort 1 (switch), no clinically significant changes from baseline through Week 48 were observed for TmP/GFR, $FEPO_4$, FEUA, or urine creatinine or for the baseline $eGFR_{CG}$ < 50 mL/min and $eGFR_{CG} \geq 50$ mL/min groups; similar results were observed for Cohort 2 (ART-naive).

**Markers of Subclinical Proximal Renal Tubulopathy**

There were no laboratory findings consistent with subclinical renal tubulopathy.

2.1.9.3.2.4. ART-Naive Adolescent Subjects

2.1.9.3.2.4.1. Study GS-US-292-0106

Renal safety for Study GS-US-292-0106 is described in detail in the CSR (GS-US-292-0106 Interim CSR, Section 11.2.4.2).

2.1.9.3.2.4.2. Renal Events

In Study GS-US-292-0106, there were no renal AEs that led to discontinuation of study drug. One subject had urinary retention of 6 days' duration reported as an SAE considered unrelated to study drug by the investigator; study drug dosing was not interrupted.

No AEs of PRT (including Fanconi syndrome) were reported.

2.1.9.3.2.4.3. Renal Laboratory Parameters

**Serum Creatinine**

The median (Q1, Q3) change from baseline in serum creatinine was 0.06 (0.00, 0.13) mg/dL at Week 1 (baseline median [Q1, Q3], 0.57 [0.50, 0.71] mg/dL). Creatinine subsequently stabilized without progressive changes; median (Q1, Q3) change from baseline at Week 24 was 0.08 (0.04, 0.17) mg/dL. No graded abnormalities of serum creatinine were reported.

**Estimated Glomerular Filtration Rate**

The median (Q1, Q3) change from baseline in eGFR (calculated using the Schwartz formula) at Week 1 was −14.0 (−27.0, −1.0) mL/min/1.73 $m^2$ (baseline median [Q1, Q3], 157.5 [133.0, 187.0] mL/min/1.73 $m^2$). The median (Q1, Q3) change from baseline at Week 24 was −20.0 (−32.0, −12.0) mL/min/1.73 $m^2$.

When eGFR was calculated using the modified Schwartz formula, the median (Q1, Q3) change from baseline at Week 2 (the first time point) was −2.6 (−8.4, 5.5) mL/min/1.73 $m^2$ (baseline median [Q1, Q3], 110.9 [95.8, 118.8] mL/min/1.73 $m^2$). The median (Q1, Q3) change from baseline at Week 24 was −5.1 (−8.2, 4.5) mL/min/1.73 $m^2$.

**Proteinuria by Urinalysis (Dipstick)**

At baseline, 2 of 48 subjects (4.2%) had Grade 1 or Grade 2 proteinuria as assessed by dipstick analysis. Postbaseline, treatment-emergent Grade 1 or Grade 2 proteinuria, generally isolated and transient, was reported for 20.9% (10 of 48 subjects).

**Proteinuria by Quantitative Assessment**

There were no clinically meaningful changes from baseline in proteinuria as assessed by UPCR (median [Q1, Q3]: baseline, 86.14 [41.49, 139.29] mg/g; percentage change at Week 24, 9.29% [−27.59%, 47.83%]).

**Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio**

A reduction from baseline was observed at Week 24 in the urine beta-2-microglobulin to creatinine ratio (median [Q1, Q3]: baseline, 179.16 [92.31, 264.71] µg/g; percentage change from baseline at Week 24, −44.61% [−72.46%, −21.00%]). No clinically meaningful change from baseline in urine RBP to creatinine ratio was observed through Week 24.

**Other Renal Biomarkers**

No clinically meaningful change from baseline in TmP/GFR, $FEPO_4$, or FEUA was observed through Week 24.

**Markers of Subclinical Proximal Renal Tubulopathy**

No subject had laboratory findings consistent with PRT.

2.1.9.3.3. RPV Studies

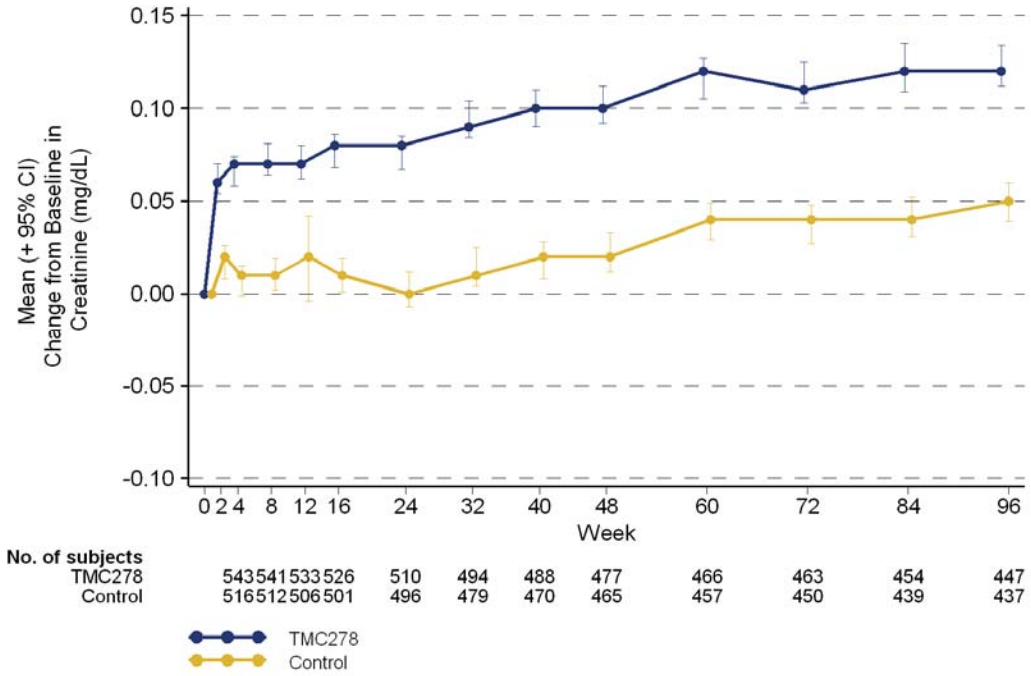
2.1.9.3.3.1. ART Naive Subjects

2.1.9.3.3.1.1. Studies C209 and C215 (FTC/TDF Subset)

2.1.9.3.3.1.1.1. Renal Laboratory Parameters

The mean change from baseline in serum creatinine over time is presented graphically by treatment group for the FTC/TDF subgroup in Figure 13.

**Figure 13. RPV Studies C209 and C213 (FTC/TDF Subset): Mean Change from Baseline in Creatinine by Background N(t)RTI Regimen (Phase 3 Week 96 Pooled Analysis)**

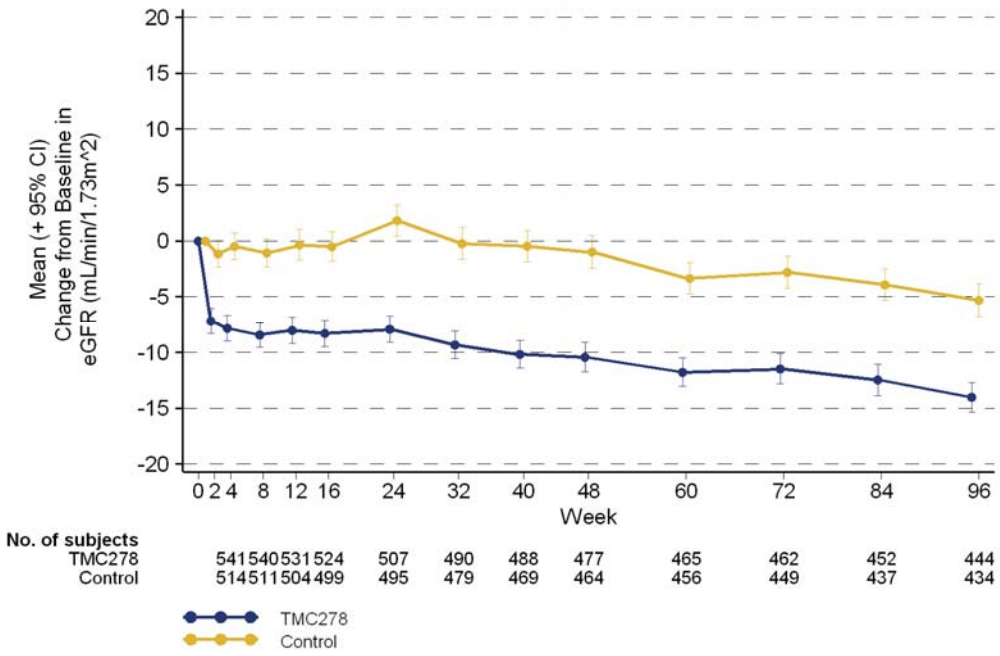



Source: TMC278-C904-W96-Anal-Saf-Lab/Display SAF.32.

Mean increases from baseline in serum creatinine values were observed for RPV-treated subjects in the FTC/TDF subgroup (0.12 mg/dL at Week 96). In the control group, small mean increases from baseline were observed with a maximum mean increase from baseline at Week 96.

Glomerular filtration rate (GFR) was calculated based on serum creatinine ($eGFR_{creat}$) using the Modification of Diet in Renal Disease (MDRD) formula {8057}. Values for mean changes from baseline in $eGFR_{creat}$ are opposite to those for serum creatinine; a mean increase from baseline in serum creatinine values represents a mean decrease from baseline in $eGFR_{creat}$ values. The mean change from baseline in $eGFR_{creat}$ over time is presented graphically for the FTC/TDF subgroup in Figure 14.

**Figure 14. RPV Studies C209 and C213 (FTC/TDF Subset): Mean Change from Baseline in $eGFR_{creat}$ by Background N(t)RTI Regimen (Phase 3 Week 96 Pooled Analysis)**




Source: TMC278-C904-W96-Anal-Saf-Lab/Display SAF.32.

The maximum mean decrease from baseline was 14.0 mL/min/1.73m$^2$ at Week 96 in the FTC/TDF subgroup. In the control group, similar to the pattern of mean change from baseline observed for the overall population, mean $eGFR_{creat}$ values fluctuated around baseline until Week 48 and then gradually decreased to Week 96 in the FTC/TDF subgroup.

The pattern of these clinical observations is similar to that observed with cimetidine, where small increases of serum creatinine reflect a direct effect on the tubular secretion of creatinine rather than a true change in renal function. Estimated glomerular filtration rate for cystatin C ($eGFR_{cyst}$) values, as a marker of glomerular filtration, showed no mean decrease but rather a small mean increase from baseline in the RPV group. This clinical observation confirmed that RPV may interfere with the tubular secretion of creatinine, but has no effect on the actual glomerular filtration. Hence, mean changes from baseline in serum creatinine and $eGFR_{creat}$ values in the RPV group are not considered clinically relevant and are not indicative of RPV-induced nephrotoxicity.

### 2.1.9.3.3.2. ART Naive Adolescent Subjects

#### 2.1.9.3.3.2.1. Study C213

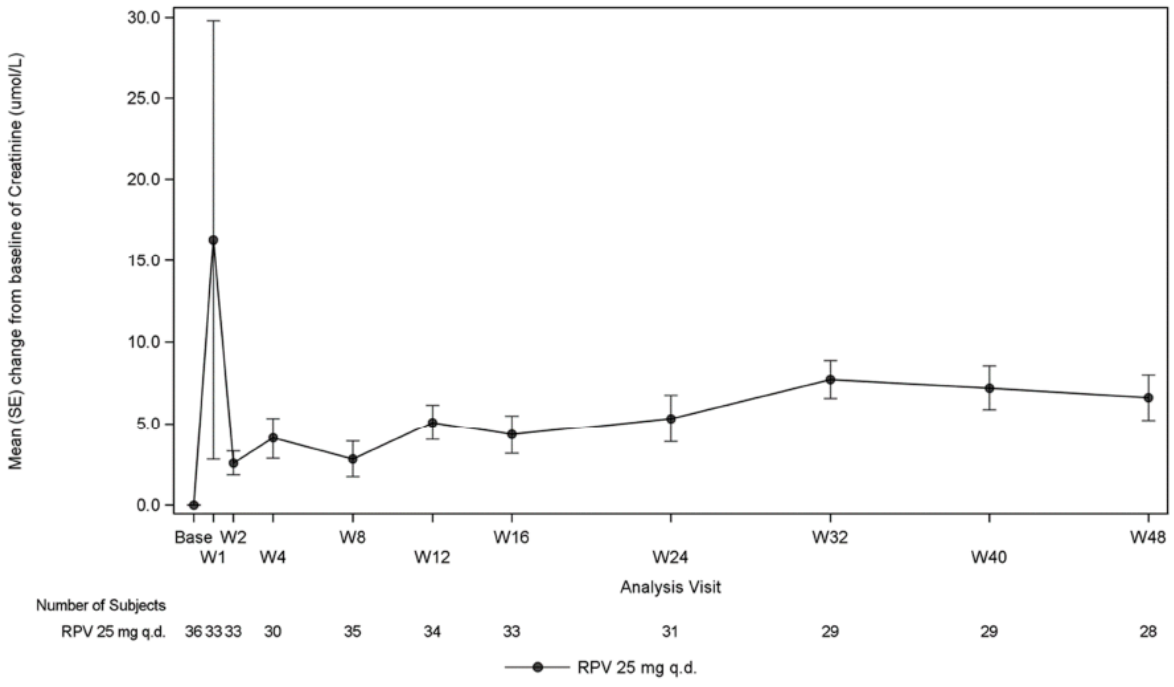
##### 2.1.9.3.3.2.1.1. Renal Laboratory Parameters

Mean changes from baseline in creatinine and glomerular filtration rate (GFR) (corrected) over time are presented in Figure 15 and Figure 16, respectively.

Mean increases from baseline in creatinine were observed at all time points in the 48-week treatment period. A maximum mean (SE) increase from baseline of 16.3 (13.49) µmol/L was observed at Week 1. At Week 48, a mean (SE) increase from baseline of 6.6 (1.39) µmol/L was observed. Note that the mean (SE) increase from baseline of 16.3 (13.49) µmol/L observed at Week 1 was due to a grade 4 creatinine increased value for one subject.

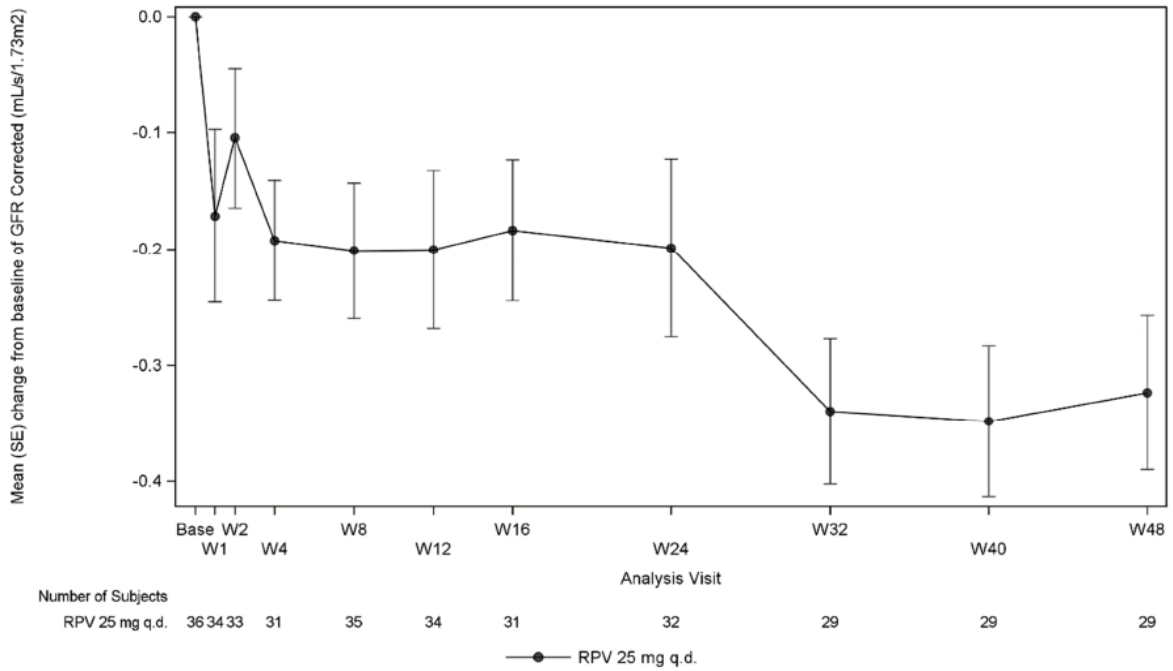
Mean decreases from baseline in GFR were observed at all time points in the 48-week treatment period. From Week 4 up to Week 24, mean (SE) decreases from baseline fluctuated between -0.18 (0.061) and -0.20 (0.058) mL/s/1.73m2, followed by a greater mean decrease from baseline at Week 32 of -0.34 (0.062) mL/s/1.73m2 which plateaued up to Week 48. At Week 48, a mean (SE) decrease from baseline of -0.32 (0.066) mL/s/1.73m2 was observed. Grade 3 hypophosphatemia was reported in 1 (2.8%) subject.

**Figure 15 RPV Study C213: Mean (SE) Changes From Baseline in Creatinine (µmol/L) Over Time (Intent-to-Treat)**




Source: TMC278-C213-W48-CSR/Figure 14

**Figure 16** **RPV Study C213: Mean (SE) Changes From Baseline in GFR Corrected (mL/s/1.73m2) Over Time (Intent-to-Treat)**




Source: TMC278-C213-W48-CSR/Figure 15

2.1.9.3.4. Complera/Eviplera Studies

2.1.9.3.4.1. Virologically Suppressed Subjects

2.1.9.3.4.1.1. Study GS-US-264-0111

2.1.9.3.4.1.1.1. Renal Events

There were AEs related to renal function in this study.

2.1.9.3.4.1.1.2. Renal Laboratory Parameters

**Serum Phosphorus**

There were no clinically relevant changes from baseline in mean values for serum phosphorus and mean values were within normal ranges in subjects receiving FTC/RPV/TDF through 48 weeks of therapy during Study GS-US-264-0111. No subject experienced a treatment-emergent Grade 3 or 4 serum phosphate laboratory abnormality or AE of serum phosphate decreased during the study.

**Serum Creatinine and Estimated Creatinine Clearance**

In Study GS-US-264-0111, serum creatinine elevations were evident by Week 4 (mean change of +0.07 mg/dL) and stable through Week 48 (mean change of +0.08 mg/dL). Two subjects ([redacted] and [redacted]) experienced treatment-emergent elevations in creatinine, both of which were transient, Grade 1 increases and were not considered AEs. No subject experienced a treatment-emergent AE of serum creatinine increased or $CL_{cr}$ decreased during the study.

Mean (SD) changes in estimated $CL_{cr}$ (by Cockcroft-Gault using observed body weight) were −7.6 (11.97) mL/min at Week 4; −8.7 (13.77) mL/min at Week 8; −12.0 (14.38) mL/min at Week 12; −14.1 (13.79) mL/min at Week 24; and −10.5 (14.90) mL/min at Week 48.

2.1.9.3.4.1.2. Study GS-US-264-0106

2.1.9.3.4.1.2.1. Renal Events

Subject [redacted] (FTC/RPV/TDF group) had a study drug-related SAE of renal impairment (Grade 2) on Day 60 that was ongoing at the end of the study. This subject had $CL_{cr}$ rates of 66.0 mL/min on Day 1, 60.4 mL/min on Day 57, 65.4 mL/min on Day 71, and 69.1−74.9 mL/min on Days 85−337 (using observed body weight in the Cockcroft-Gault formula). Concurrent AEs included glycosuria and proteinuria (both Grade 1). The subject was permanently discontinued from the study due to the events of renal impairment and proteinuria. An SAE of nephropathy toxic (Grade 2) was reported in 1 subject (Subject [redacted]) in the FTC/RPV/TDF group on Day 262 (ongoing at the end of the study). This event was considered to be related to study drug. This subject had $CL_{cr}$ rates of 75.0 mL/min on Day 1, 71.2 mL/min on Day 254, 73.9 mL/min on Day 338, and 75.2 mL/min on Day 421 (using observed body weight in the Cockcroft-Gault formula). No action was taken with the study drug.

2.1.9.3.4.1.2.2. Renal Laboratory Parameters

**Serum Phosphorus**

There were no clinically relevant changes from baseline in mean values for serum phosphorus and mean values were within normal ranges throughout the study in all treatment groups (FTC/RPV/TDF group [Weeks 0−48], SBR [Weeks 0−24], and Delayed Switch [Weeks 25−48]) during Study GS-US-264-0106. No subject experienced a treatment-emergent Grade 3 or 4 serum phosphate laboratory abnormality or AE of serum phosphate decreased during the study.

**Serum Creatinine and Estimated Creatinine Clearance**

Overall, serum creatinine elevations, and decreases in estimated $CL_{cr}$ (by Cockcroft-Gault using observed or ideal body weight) and eGFR, were evident by Week 4 and stable through Week 24 in subjects receiving FTC/RPV/TDF compared to subjects remaining on their baseline ARV regimen (SBR group) during Study GS-US-264-0106. At study baseline, mean (SD) serum creatinine was 1.00 (0.180) mg/dL in the FTC/RPV/TDF group and 1.01 (0.163) mg/dL in the SBR group; mean (SD) estimated $CL_{cr}$ using Cockcroft-Gault (observed body weight) was 109.5 (28.38) mL/min in the FTC/RPV/TDF group and 108.6 (29.94) mL/min in the SBR group.

At Week 4, the mean (SD) increase in serum creatinine was 0.04 (0.107) mg/dL in the FTC/RPV/TDF group and 0.01 (0.091) mg/dL in the SBR group. The mean (SD) change in estimated $CL_{cr}$ (using observed body weight) was –3.5 (11.39) mL/min in the FTC/RPV/TDF group and –0.7 (10.64) mL/min in the SBR group.

At Week 24, statistically significant differences between the FTC/RPV/TDF and SBR groups were observed in the mean changes from baseline in serum creatinine (0.05 vs. 0.01 mg/dL [$p < 0.001$]), estimated $CL_{cr}$ (using observed body weight; –4.4 vs. 0.1 mL/min [$p = 0.001$]), and eGFR (–4.5 vs. –0.5 mL/min/1.73 $m^2$ [$p < 0.001$]). Similar changes in these renal function parameters were observed in the Delayed Switch group over 24 weeks of FTC/RPV/TDF therapy. The increase in serum creatinine and decrease in estimated $CL_{cr}$ and eGFR were generally maintained through Week 48 in the FTC/RPV/TDF group.

When these renal function parameters (serum creatinine, estimated $CL_{cr}$, and eGFR) were analyzed in subjects using TDF at baseline and subjects receiving non-TDF regimens at baseline, similar trends were observed.

2.1.9.3.5. FTC/RPV/TAF Studies

**Study GS-US-366-1159**

There were AEs related to renal function in this study.

Median (Q1, Q3) baseline serum creatinine was 0.9 (0.8, 1.0) mg/dL prior to all treatments. Median (Q1, Q3) changes from baseline at Day 14 were as follows: 0.0 (0.0, 0.1) mg/dL following FTC/RPV/TAF, 0.1 (0.1, 0.1) mg/dL following RPV, 0.0 (0.0, 0.1) mg/dL following E/C/F/TAF.

Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: 117.18 (102.48, 133.22) mL/min prior to FTC/RPV/TAF, 117.09 (101.60, 134.23) mL/min prior to RPV, and 117.78 (106.72, 132.90) mL/min prior to E/C/F/TAF. Median (Q1, Q3) changes from baseline at Day 14 were as follows: −2.11 (−10.96, 0.00) mL/min following FTC/RPV/TAF, −1.26 (−12.23, 0.28) mL/min following RPV, and −2.00 (−10.36, 0.51) following E/C/F/TAF.

Overall, proteinuria was reported for 10 subjects (10.4%); 9 subjects (9.4%) had Grade 1 proteinuria (FTC/RPV/TAF 3 subjects, 3.2%; RPV 2 subjects, 2.1%, E/C/F/TAF 4 subjects, 4.2%) and 1 subject had Grade 2 proteinuria following E/C/F/TAF.

**Study GS-US-366-1651**

There were AEs related to renal function in this study.

Median (Q1, Q3) baseline $eGFR_{CG}$ was 113.1 (99.5, 128.3) mL/min. There were no clinically relevant changes from baseline in renal laboratory parameters during this single-dose study (serum creatinine, $eGFR_{CG}$, or proteinuria).

**Study GS-US-366-1689**

There were AEs related to renal function in this study.

Median (Q1, Q3) baseline (predose) serum creatinine was 1.0 (0.8, 1.1) mg/dL. Median (Q1, Q3) changes from baseline at Day 11/12 were as follows: 0.0 (0.0, 0.1) mg/dL following LDV/SOF, and 0.1 (0.0, 0.2) mg/dL following treatment with both FTC/RPV/TAF and LDV/SOF+FTC/RPV/TAF.

Median (Q1, Q3) baseline (predose) $eGFR_{CG}$ values was 122.01 (107.90, 135.57) mL/min. Median (Q1, Q3) changes from baseline at Day 11/12 were as follows: −4.50 (−17.58, −1.82) mL/min following LDV/SOF, −12.76 (−23.88, −1.79) mL/min following FTC/RPV/TAF, and −14.38 (−25.46, −4.50) following LDV/SOF+FTC/RPV/TAF.

Proteinuria was reported for 3 subjects (7.1%) who received LDV/SOF and 2 subjects (4.8%) who received LDV/SOF+FTC/RPV/TAF, all of which were Grade 1.

2.1.9.4. Ocular Safety

In a 9-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12-18 mg/kg) had minimal mononuclear cell infiltration in the posterior uvea. This finding did not occur in animals given lower doses, and it has not occurred in other animal studies. This nonclinical finding has also not been observed in humans, where the dose is much lower, nor have there been reports of posterior uveitis in human clinical studies.

Across all E/C/F/TAF studies, eye disorders were uncommon, balanced between treatment arms, and were considered by the investigator as unrelated to the study drugs. None were indicative of posterior uveitis, and none resulted in permanent discontinuation of study drugs. One subject in Study GS-US-292-0106 had an AE of intermediate uveitis that was considered related to study drug by the investigator but was resolving while the subject continued on study drug without interruption.

2.1.9.4.1. E/C/F/TAF Studies

2.1.9.4.2. Methodology

Any ophthalmic AE reported by subjects who received at least 1 dose of study drug in the E/C/F/TAF studies was included in an analysis using the SOC term eye disorders, which includes all AEs related to the eye. An additional analysis was performed to detect AEs where the symptoms reported may potentially represent posterior uveitis. This was done by selecting a subset of nonspecific eye disorder PTs, and this list of terms was reviewed and edited by an external ophthalmologist for comprehensiveness.

Specific ocular toxicity monitoring was not included in the studies of FTC, RPV, or FTC/RPV/TDF. Therefore, ocular safety data are presented below only for E/C/F/TAF.

#### 2.1.9.4.2.1. ART-Naive Subjects

##### 2.1.9.4.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

The incidence of AEs in the eye disorders SOC across Studies GS-US-292-0104 and GS-US-292-0111 was similar for both treatment groups (E/C/F/TAF 7.0%, 61 subjects; STB 7.3%, 63 subjects; Table 57).

Sixteen subjects (1.8%) in the E/C/F/TAF group and 9 subjects (1.0%) in the STB group had AEs in the eye disorders SOC considered related to study drugs by the investigator (E/C/F/TAF ISS, Table 11). One subject in each treatment group had AEs in the eye disorders SOC resulting in discontinuation of study drugs, one of which was also reported as an SAE (for the subject in the STB group (E/C/F/TAF ISS, Table 16). Subject [redacted], in the E/C/F/TAF group in Study GS-US-292-0111, had 3 nonserious AEs of Grade 2 eye irritation, eye pain, and eye pruritus. All 3 AEs were considered related to study drugs by the investigator. Subject [redacted], in the STB group, had an SAE of Grade 2 iridocyclitis considered unrelated to study drugs by the investigator. Subject [redacted], in the STB group, also had an SAE of Grade 2 retinal detachment considered unrelated to study drugs by the investigator; treatment with study drugs continued. Additionally, Subject [redacted] in the E/C/F/TAF group in Study GS-US-292-0104 had an SAE of retinal detachment following trauma considered unrelated to study drugs by the investigator.

There were no AEs of uveitis in the E/C/F/TAF group in either study (E/C/F/TAF ISS, Table 7). There was 1 uveitis event reported in the STB group in Study GS-US-292-0111 (iridocyclitis, reported as right and left sided anterior uveitis, detailed above). Twenty-three subjects (2.7%) in the E/C/F/TAF group and 15 subjects (1.7%) in the STB group had AEs from the list of identified terms that could represent symptoms of uveitis (E/C/F/TAF ISS, Table 17). The most common potential uveitis AE was vision blurred (E/C/F/TAF 1.3%, 11 subjects; STB 1.0%, 9 subjects). Blurred vision was considered related to study drugs by the investigator for 4 subjects (0.5%) in the E/C/F/TAF group, and 3 subjects (0.3%) in the STB group (E/C/F/TAF ISS, Table 11). Other than the SAE of iridocyclitis detailed above; all other potential uveitis AEs were nonserious, Grade 1 or 2, and did not result in discontinuation of study drugs (E/C/F/TAF ISS, Tables 10, 14, 16, and 17). Other than the SAE of iridocyclitis in the STB group, no other potential uveitis AEs were considered representative of an actual clinical case of uveitis.

**Table 57. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Adverse Events: Eye Disorders (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | E/C/F/TAF (N=866) | STB (N=867) |
|---|---|---|
| Eye disorders | 61 (7.0%) | 63 (7.3%) |
| Vision blurred | 11 (1.3%) | 9 (1.0%) |
| Eye pain | 7 (0.8%) | 8 (0.9%) |
| Dry eye | 3 (0.3%) | 10 (1.2%) |
| Eye irritation | 6 (0.7%) | 2 (0.2%) |
| Eye pruritus | 3 (0.3%) | 5 (0.6%) |
| Conjunctivitis allergic | 3 (0.3%) | 4 (0.5%) |
| Blepharitis | 2 (0.2%) | 4 (0.5%) |
| Chalazion | 3 (0.3%) | 2 (0.2%) |
| Visual acuity reduced | 3 (0.3%) | 2 (0.2%) |
| Blepharospasm | 1 (0.1%) | 3 (0.3%) |
| Ocular hyperaemia | 2 (0.2%) | 2 (0.2%) |
| Photophobia | 3 (0.3%) | 1 (0.1%) |
| Visual impairment | 4 (0.5%) | 0 |
| Astigmatism | 1 (0.1%) | 1 (0.1%) |
| Cataract | 1 (0.1%) | 1 (0.1%) |
| Conjunctival hyperaemia | 1 (0.1%) | 1 (0.1%) |
| Eye discharge | 0 | 2 (0.2%) |
| Lacrimation increased | 2 (0.2%) | 0 |
| Periorbital oedema | 1 (0.1%) | 1 (0.1%) |
| Pterygium | 0 | 2 (0.2%) |
| Retinal detachment | 1 (0.1%) | 1 (0.1%) |
| Vitreous floaters | 1 (0.1%) | 1 (0.1%) |
| Abnormal sensation in eye | 0 | 1 (0.1%) |
| Asthenopia | 1 (0.1%) | 0 |
| Blepharitis allergic | 1 (0.1%) | 0 |
| Blindness | 0 | 1 (0.1%) |
| Conjunctival haemorrhage | 1 (0.1%) | 0 |
| Conjunctival pallor | 1 (0.1%) | 0 |
| Dark circles under eyes | 1 (0.1%) | 0 |
| Exophthalmos | 0 | 1 (0.1%) |

| Adverse Events by System Organ Class and Preferred Term | E/C/F/TAF (N=866) | STB (N=867) |
|---|---|---|
| Eye allergy | 0 | 1 (0.1%) |
| Eye disorder | 0 | 1 (0.1%) |
| Eye swelling | 0 | 1 (0.1%) |
| Eyelid oedema | 0 | 1 (0.1%) |
| Eyelid rash | 1 (0.1%) | 0 |
| Glaucoma | 1 (0.1%) | 0 |
| Iridocyclitis | 0 | 1 (0.1%) |
| Photopsia | 0 | 1 (0.1%) |
| Strabismus | 0 | 1 (0.1%) |
| Vitritis | 1 (0.1%) | 0 |

Adverse events were coded using MedDRA 17.0.
System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: E/C/F/TAF ISS Table 7

#### 2.1.9.4.2.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, AEs in the eye disorders SOC were reported for 7.1% of subjects (n = 8) in the E/C/F/TAF group (Table 58). No AE in the eye disorders SOC was reported in the STB group.

One nonserious AE of photophobia reported for Subject [redacted] in the E/C/F/TAF group was considered related to study drugs by the investigator (further details below). All other eye disorder AEs were considered not related to study drugs by the investigator. All eye disorder AEs resolved without treatment and none resulted in discontinuation of study drugs.

**Table 58. E/C/F/TAF Study GS-US-292-0102: Summary of Adverse Events: Eye Disorders (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a,b,c,d] | E/C/F/TAF (N=112) | STB (N=58) | p-value[e] |
|---|---|---|---|
| Eye disorders | 8 (7.1%) | 0 | 0.052 |
| Vision blurred | 2 (1.8%) | 0 | |
| Conjunctival haemorrhage | 1 (0.9%) | 0 | |
| Diplopia | 1 (0.9%) | 0 | |
| Lacrimation increased | 1 (0.9%) | 0 | |
| Photophobia | 1 (0.9%) | 0 | |
| Retinal detachment | 1 (0.9%) | 0 | |
| Visual impairment | 1 (0.9%) | 0 | |

a Adverse events were coded using MedDRA 17.0.
b Preferred term was presented by descending order of the total frequencies.
c Eye disorder was defined to be any event with SOC of Eye Disorders.
d Only PTs with at least 1 subject having the event in any treatment group are presented in this table.
e p-value was from the Fisher exact test.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table Req6674.1

In the SOC of infections and infestations, conjunctivitis was reported for 8.0% of subjects (n = 9) in the E/C/F/TAF group and no subjects in the STB group. All AEs of conjunctivitis were Grade 1 or Grade 2, were nonserious, and resolved without interruption to, or discontinuation of, study drugs. No AE of conjunctivitis was considered related to study drugs by the investigator.

Four subjects in the E/C/F/TAF group had AEs from the list of identified terms that could represent symptoms of anterior or posterior uveitis, none of which resulted in discontinuation of study drugs. These were as follows:

- Subject [redacted]: a 35-year-old female, had Grade 1 blurred vision on Day 285 that was considered unrelated to study drugs by the investigator and resolved on Day 290 without treatment.
- Subject [redacted]: a 26-year-old male, had Grade 1 blurred vision and fatigue that began after the first dose of study drugs. The events were considered unrelated to study drugs by the investigator and resolved within 1 month without treatment (exact dates not reported).
- Subject [redacted]: a 28-year-old male had Grade 1 photophobia (reported as “intermittent light sensitivity”) as well as Grade 1 diarrhea, vomiting, nausea, decreased appetite, headache, and hot flush, which all began on Day 2. All of these AEs were considered related to study drugs by the investigator. The event of photophobia resolved on Day 38 without treatment.

- Subject [redacted]: a 40-year-old male had Grade 1 visual impairment (clinically documented as "decreased near vision"; AE reported as "unspecified visual disturbance") on Day 398 (continuing). The event was considered unrelated to study drugs by the investigator. The subject was referred to an ophthalmologist but did not follow up with the referral. The subject's last study visit was Day 642. No further information on the event of visual impairment is available.

2.1.9.4.2.2. Virologically Suppressed Subjects

2.1.9.4.2.2.1. Study GS-US-292-0109

In Study GS-US-292-0109, AEs in the SOC of eye disorders were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 5.5%, 53 of 959 subjects; FTC/TDF+3rd Agent 4.6%, 22 of 477 subjects; Table 59).

Subject [redacted] in the E/C/F/TAF group had an SAE of retinal detachment with onset on Day 167; the event resolved with treatment on Day 168. This SAE was considered by the investigator as unrelated to the study drug and did not result in discontinuation of the study drug. This subject had a history of retinal detachment.

Nonserious AEs reported for 2 subjects in the E/C/F/TAF group and for 5 subjects in the FTC/TDF+3rd Agent group were considered by the investigator as related to study drugs. In the E/C/F/TAF group, Subject [redacted] had two Grade 1 AEs of visual acuity reduced and vision blurred, with exact onset dates unknown; and Subject [redacted] had a Grade 1 AE of vision blurred with onset on Day 279. All 3 events were listed as ongoing at the time of the data cut date for this study, and none resulted in discontinuation of study drug. In the FTC/TDF+3rd Agent group, ocular icterus was reported for 5 subjects taking ATV/boosted+TVD regimens: Subjects [redacted] (Grade 1, onset Day 252), [redacted] (Grade 1, onset Day 85), [redacted] (Grade 1, onset Day 174), [redacted] (Grade 1, onset Day 295), and [redacted] (Grade 2, exact onset date unknown). Four of these events were listed as ongoing at the time of the writing of this summary document, and none resulted in discontinuation of study drug.

All other eye disorder AEs were considered by the investigator as not related to study drugs. Most eye disorder AEs resolved and none resulted in discontinuation of study drugs.

**Table 59. E/C/F/TAF Study GS-US-292-0109: Summary of Adverse Events in the SOC of Eye Disorders (Safety Analysis Set)**

| Adverse Events by Preferred Term[a,b,c,d] | E/C/F/TAF (N=959) | FTC/TDF+3rd Agent (N=477) |
|---|---|---|
| Number of Subjects Experiencing Any Eye Disorders | 53 (5.5%) | 22 (4.6%) |
| Vision Blurred | 10 (1.0%) | 1 (0.2%) |
| Ocular Icterus | 1 (0.1%) | 7 (1.5%) |
| Eye Irritation | 4 (0.4%) | 1 (0.2%) |
| Blepharospasm | 3 (0.3%) | 1 (0.2%) |
| Conjunctival Haemorrhage | 2 (0.2%) | 2 (0.4%) |
| Vitreous Floaters | 1 (0.1%) | 3 (0.6%) |
| Cataract | 3 (0.3%) | 0 |
| Conjunctivitis Allergic | 2 (0.2%) | 1 (0.2%) |
| Visual Impairment | 3 (0.3%) | 0 |
| Chalazion | 2 (0.2%) | 0 |
| Dacryostenosis Acquired | 1 (0.1%) | 1 (0.2%) |
| Eye Discharge | 2 (0.2%) | 0 |
| Ocular Discomfort | 2 (0.2%) | 0 |
| Ocular Hyperaemia | 1 (0.1%) | 1 (0.2%) |
| Visual Acuity Reduced | 2 (0.2%) | 0 |
| Arcus Lipoides | 1 (0.1%) | 0 |
| Astigmatism | 0 | 1 (0.2%) |
| Blepharitis | 1 (0.1%) | 0 |
| Blindness | 1 (0.1%) | 0 |
| Corneal Scar | 1 (0.1%) | 0 |
| Diplopia | 1 (0.1%) | 0 |
| Eye Allergy | 1 (0.1%) | 0 |
| Eye Pain | 1 (0.1%) | 0 |
| Eye Pruritus | 1 (0.1%) | 0 |
| Eyelid Oedema | 1 (0.1%) | 0 |
| Glare | 1 (0.1%) | 0 |
| Keratitis | 0 | 1 (0.2%) |
| Lacrimation Increased | 1 (0.1%) | 0 |
| Macular Hole | 0 | 1 (0.2%) |

| Adverse Events by Preferred Term[a,b,c,d] | E/C/F/TAF (N=959) | FTC/TDF+3rd Agent (N=477) |
|---|---|---|
| Mydriasis | 1 (0.1%) | 0 |
| Myopia | 0 | 1 (0.2%) |
| Optic Disc Disorder | 0 | 1 (0.2%) |
| Panophthalmitis | 1 (0.1%) | 0 |
| Photophobia | 1 (0.1%) | 0 |
| Pigment Dispersion Syndrome | 1 (0.1%) | 0 |
| Presbyopia | 1 (0.1%) | 0 |
| Pterygium | 1 (0.1%) | 0 |
| Retinal Detachment | 1 (0.1%) | 0 |
| Scleral Hyperaemia | 1 (0.1%) | 0 |
| Ulcerative Keratitis | 1 (0.1%) | 0 |

a Adverse events were coded using MedDRA 17.0.
b Preferred term was presented by descending order of the total frequencies.
c Eye disorder was defined as any event within the SOC of eye disorders.
d Only PTs with at least 1 subject having the event in any treatment group are presented in this table.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 22

There were no reports of uveitis during the study. Adverse events from a list of identified terms that could represent symptoms of uveitis were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 1.9%; FTC/TDF+3rd Agent 0.8%). These events were all Grade 1 or 2 and none resulted in discontinuation of study drugs. Two subjects in the E/C/F/TAF group had nonspecific ocular AEs (Subjects [redacted] [visual acuity reduced and vision blurred] and [redacted] [vision blurred]) that were considered by the investigator as related to study drug.

Among the subjects who participated in the ophthalmologic substudy (E/C/F/TAF 32 subjects; FTC/TDF+3rd Agent 15 subjects), most had normal ophthalmologic central reading assessments at baseline (E/C/F/TAF 25 subjects; FTC/TDF+3rd Agent 13 subjects). Of the subjects with available postbaseline data, most had normal assessments at Week 24 (E/C/F/TAF 26 of 31 subjects; FTC/TDF+3rd Agent 12 of 14 subjects) and Week 48 (E/C/F/TAF 14 of 18 subjects; FTC/TDF+3rd Agent 6 of 8 subjects). Subject [redacted] in the E/C/F/TAF group had a shift from normal at baseline to abnormal at Week 24 in the central reading assessment due to the detection of a retinal hemorrhage in the left eye. No subjects in the ophthalmic substudy had fundoscopic findings consistent with uveitis.

2.1.9.4.2.2.2. Study GS-US-292-0102 Open-Label Extension

Few subjects in the switch groups of Study GS-US-292-0102 had ocular AEs in the SOC of eye disorders.

#### 2.1.9.4.2.3. Subjects with Mild to Moderate Renal Impairment

##### 2.1.9.4.2.3.1. Study GS-US-292-0112

In Study GS-US-292-0112, AEs in the eye disorders SOC were reported in 22 of 242 subjects (9.1%) in Cohort 1 (switch) (6 of 80 subjects [7.5%] with baseline $eGFR_{CG} < 50$ mL/min and 16 of 162 [9.9%] of subjects with baseline $eGFR_{CG} \geq 50$ mL/min) and no subjects in Cohort 2 (ART-naive). None of the AEs in the eye disorders SOC were serious or resulted in discontinuation of study drug. Two ocular AEs reported for 1 subject (vitreous floaters and photopsia; Subject [redacted]) were considered related to study drugs by the investigator. All other ocular AEs were considered unrelated to the study drugs by the investigator.

Four Cohort 1 subjects, 3 with baseline $eGFR_{CG} \geq 50$ mL/min and 1 with baseline $eGFR_{CG} < 50$ mL/min, had AEs from the list of identified terms that could represent symptoms of uveitis, none of which resulted in discontinuation of study drug.

None of these AEs were considered representative of an actual case of clinical uveitis.

#### 2.1.9.4.2.4. ART-Naive Adolescent Subjects

##### 2.1.9.4.2.4.1. Study GS-US-292-0106

In Study GS-US-292-0106, Subject [redacted], a 13-year-old [redacted] female, had Grade 3 intermediate uveitis. This subject had been infected with HIV-1 via vertical transmission, and entered the study with a baseline CD4 cell count of 1110 cells/μL. At Day 14 the subject presented with visual field changes and conjunctival hyperemia. Grade 3 chorioretinitis was reported as low-grade posterior uveitis considered related to study drug by the investigator. Symptoms improved significantly with antibiotic/steroid and nonsteroidal anti-inflammatory eye drops, and oral steroid and antihistamine therapy. Concurrent eye disorders reported on Day 14 were Grade 1 allergic conjunctivitis, and Grade 2 visual impairment (reported as an SAE considered related to study drug by the investigator) and cataracts. Following repeat fundoscopic examination on Day 27, the chorioretinitis was reassessed as Grade 2 intermediate uveitis, reported as an SAE, and still considered related to study drug by the investigator. Throughout, the subject continued on study drug without interruption. At the time of the data cut for the Week 24 analysis, intermediate uveitis was ongoing but resolving; visual impairment and recurrent allergic conjunctivitis were ongoing, and the subject was continuing on study drug.

The only other AEs within the Eye Disorders SOC were Grade 1 allergic conjunctivitis and giant papillary conjunctivitis, both considered unrelated to study drug by the investigator, in 1 subject.

### 2.1.9.5. Cardiovascular Safety

Supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG. There is no evidence of cardiac conduction abnormalities in studies with E/C/F/TAF to date.

#### 2.1.9.5.1. E/C/F/TAF Studies

Detailed information on vital signs, physical findings, and other observations related to safety may be found in the respective CSRs for each study (GS-US-292-0104 Week 48 CSR, Section 11.7; GS-US-292-0111 Week 48 CSR, Section 11.7; GS-US-292-0102 Week 96 CSR, Section 11.7; GS-US-292-0109 Week 48 CSR, Section 11.8; GS-US-292-0112 Week 24 CSR, Section 11.8; and GS-US-292-0106 Interim CSR, Section 11.7).

##### 2.1.9.5.1.1. ART-Naive Subjects

###### 2.1.9.5.1.1.1. Studies GS-US-292-0104 and GS-US-292-0111

In Study GS-US-292-0104, clinically significant ECG abnormalities were reported for 2 subjects in the E/C/F/TAF group and 1 subject in the STB group. Clinically significant ECG abnormalities were reported as an AE for 1 subject in the E/C/F/TAF group. Subject [redacted], who had a normal ECG at baseline, had clinically significant abnormal sinus rhythm with sinus arrhythmia and first degree atrioventricular block at Week 48, which was also reported as a nonserious AE of ECG abnormal considered. The event was ongoing at the time of the data cutoff, considered unrelated to study drugs by the investigator, and did not result in discontinuation of study drugs.

In Study GS-US-292-0111, clinically significant ECG abnormalities were reported as an AE for 1 subject in the E/C/F/TAF group. Subject [redacted], who had an abnormal ECG at baseline (premature supraventricular complexes with aberrant ventricular conduction), had clinically significant atrial fibrillation on Day 305, which was reported as a nonserious AE of ECG abnormal. The event resolved the same day, was considered unrelated to study drugs by the investigator, and did not result in discontinuation of study drugs.

###### 2.1.9.5.1.1.2. Study GS-US-292-0102

There were no clinically significant ECG findings reported for subjects during the randomized phase of Study GS-US-292-0102.

Two subjects in the E/C/F/TAF group had AEs related to ECG findings: Subject [redacted] had a nonserious ST segment elevation concurrent with pericarditis, sinus bradycardia, and upper respiratory tract infection; Subject [redacted] had a nonserious ECG abnormality that was not associated with any AE. Neither event was related to study drugs or resulted in discontinuation of study treatment.

There were no clinically significant ECG findings reported for subjects in the E/C/F/TAF group in the extension phase.

#### 2.1.9.5.1.2. Virologically Suppressed Subjects in E/C/F/TAF Studies

##### 2.1.9.5.1.2.1. Study GS-US-292-0109

In Study GS-US-292-0109, clinically significant ECG findings were reported for 6 subjects in the E/C/F/TAF group and 1 subject in the FTC/TDF+3rd Agent group. These ECG findings were reported as AEs for 2 subjects in the E/C/F/TAF group. Subject [redacted] in the E/C/F/TAF group, with normal ECG at baseline, had clinically significant abnormal nonspecific ST and T wave abnormality, with normal sinus rhythm on Day 331. The wave abnormality was reported as a nonserious, Grade 1 AE of ECG abnormal. The event was ongoing at the time of the data cutoff, considered by the investigator as unrelated to study drug, and did not result in discontinuation of study drug. Subject [redacted] in the E/C/F/TAF group, with normal ECG at baseline, had clinically significant abnormal sinus rhythm with possible premature atrial complexes, aberrant conduction, possible left atrial enlargement, and incomplete right bundle branch block on Day 333. The bundle branch block right and arrhythmia were reported as nonserious, Grade 1 AEs. The events were ongoing at the time of the data cutoff, were considered by the investigator as unrelated to study drug, and did not result in discontinuation of study drug.

In addition, 5 subjects in the E/C/F/TAF group and 3 subjects in the FTC/TDF+3rd Agent group had AEs related to ECG findings. In the E/C/F/TAF group, the AEs were supraventricular extrasystoles and atrial fibrillation (both reported for Subject [redacted]), sinus tachycardia (Subject [redacted]), tachycardia (Subject [redacted]), and sinus bradycardia (reported for Subjects [redacted] and [redacted]). In the FTC/TDF+3rd Agent group, the reported AEs were extrasystoles (Subject [redacted]), arrhythmia (Subject [redacted]), and sinus bradycardia (Subject [redacted]). All of these AEs were nonserious and Grade 1 or 2; none led to discontinuation of study drugs. The AEs of supraventricular extrasystoles and atrial fibrillation reported for Subject [redacted] in the E/C/F/TAF group were assessed as related to study drug by the investigator.

##### 2.1.9.5.1.2.2. Study GS-US-292-0102 Open-Label Extension

There were no clinically significant ECG findings or AEs related to ECG findings reported for subjects in the switch groups.

#### 2.1.9.5.1.3. Subjects with Mild to Moderate Renal Impairment

##### 2.1.9.5.1.3.1. Study GS-US-292-0112

There were no clinically significant ECG findings reported in Study GS-US-292-0112.

A total of 14 Cohort 1 switch subjects and 1 Cohort 2 ART-naive subject had AEs related to ECGs or cardiac conditions. Of those, 1 Cohort 1 switch subject had an AE related to ECGs or cardiac conditions that was considered by the investigator to be related to study drug (intermittent palpitations on study Day 4 non-serious and resolved within 4 days of onset).

#### 2.1.9.5.1.4. ART-Naive Adolescent Subjects

##### 2.1.9.5.1.4.1. Study GS-US-292-0106

Physical examination data were not collected in eCRFs for Study GS-US-292-0106. There were no clinically relevant changes in any vital signs parameter in any subject during the study.

### 2.1.9.5.2. RPV Studies

#### 2.1.9.5.2.1. ART-Naive Subjects

##### 2.1.9.5.2.1.1. Studies C209 and C215

Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

###### 2.1.9.5.2.1.1.1. Events of Interest Potentially Related to QT Interval Prolongation

Events of interest potentially related to QT interval prolongation are summarized in Table 60.

**Table 60. RPV Studies C209 and C215: Summary of Treatment-Emergent Events of Interest Potentially Related to QT Interval Prolongation (Phase 3 Week 96 Pooled Analysis)**

| | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| **AE summary** | **RPV N = 346** | **Control N = 344** | **RPV N = 340** | **Control N = 338** | **RPV N = 686** | **Control N = 682** |
| **Treatment duration [weeks], median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any, n (%)** | **1 (0.3)** | **4 (1.2)** | **3 (0.9)** | **14 (4.1)** | **4 (0.6)** | **18 (2.6)** |
| Grade 1 | 1 (0.3) | 2 (0.6) | 2 (0.6) | 10 (3.0) | 3 (0.4) | 12 (1.8) |
| Grade 2 | 0 | 1 (0.3) | 0 | 3 (0.9) | 0 | 4 (0.6) |
| Grade 3 | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.1) | 2 (0.3) |
| **Time to onset of first treatment-emergent event [days]** | | | | | | |
| Number of events | 1 | 4 | 2 | 14 | 3 | 18 |
| Median (range) | 195.0 (195 - 195) | 287.5 (29 - 589) | 557.5 (351 - 764) | 414.0 (165 - 673) | 351.0 (195 - 764) | 414.0 (29 - 673) |
| **Duration [days]** | | | | | | |
| Number of events | 1 | 4 | 1 | 14 | 2 | 18 |
| Median (range) | 7.0 (7 - 7) | 1.0 (1 - 16) | 32.0 (32 - 32) | 83.5 (1 - 200) | 19.5 (7 - 32) | 36.5 (1 - 200) |
| **Treatment-related[a] AE, n (%)** | **0** | **2 (0.6)** | **2 (0.6)** | **10 (3.0)** | **2 (0.3)** | **12 (1.8)** |
| **Leading to permanent discontinuation, n (%)** | **0** | **0** | **1 (0.3)** | **0** | **1 (0.1)** | **0** |

a Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.
No events of interest potentially related to QT interval prolongation were reported as SAEs or led to temporary discontinuation.
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.3, Display SAF.25, Display SAF.26, and Display GEN.13.

There were 4 subjects [0.6%] in the RPV group and 18 subjects [2.6%] in the control group reported with events of interest potentially related to QT interval prolongation in the Week 96 pooled analysis.

Overall, the incidence of events of interest potentially related to QT interval prolongation was low and reported with similar grades. Events of interest potentially related to QT interval prolongation were reported to be treatment-related in 0.3% (2 subjects) in the RPV group compared with 1.8% in the control group. Too few events of interest potentially related to QT interval prolongation were reported for meaningful conclusions to be drawn concerning the time to onset and duration of these events.

No event of interest potentially related to QT interval prolongation was reported as an SAE.

One female subject in the RPV group had an event of interest potentially related to QT interval prolongation that led to permanent discontinuation. This subject had a Grade 3 prolonged ECG QT interval at Week 48 (QTcF at Week 48 was 457 ms, an increase from baseline of 77 ms). The AE was reported to be probably related to study medication by the investigator.

Events of interest potentially related to QT interval prolongation were reported at very low incidence throughout the 96-week treatment period. These events did not occur more notably at any particular time period.

The incidence of events of interest potentially related to QTc prolongation is summarized in Table 61.

**Table 61. RPV Studies C209 and C215: Treatment-Emergent Events of Interest Potentially Related to QT Interval Prolongation (Regardless of Severity and Drug Relatedness) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Any event of interest potentially related to QT interval prolongation** | **1 (0.3)** | **4 (1.2)** | **3 (0.9)** | **14 (4.1)** | **4 (0.6)** | **18 (2.6)** |
| **Nervous System Disorders** | **1 (0.3)** | **3 (0.9)** | **1 (0.3)** | **3 (0.9)** | **2 (0.3)** | **6 (0.9)** |
| Syncope | 1 (0.3) | 3 (0.9) | 0 | 3 (0.9) | 1 (0.1) | 6 (0.9) |
| Loss of consciousness | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| **Investigations** | **0** | **1 (0.3)** | **2 (0.6)** | **11 (3.3)** | **2 (0.3)** | **12 (1.8)** |
| ECG QT prolonged | 0 | 1 (0.3) | 2 (0.6) | 11 (3.3) | 2 (0.3) | 12 (1.8) |

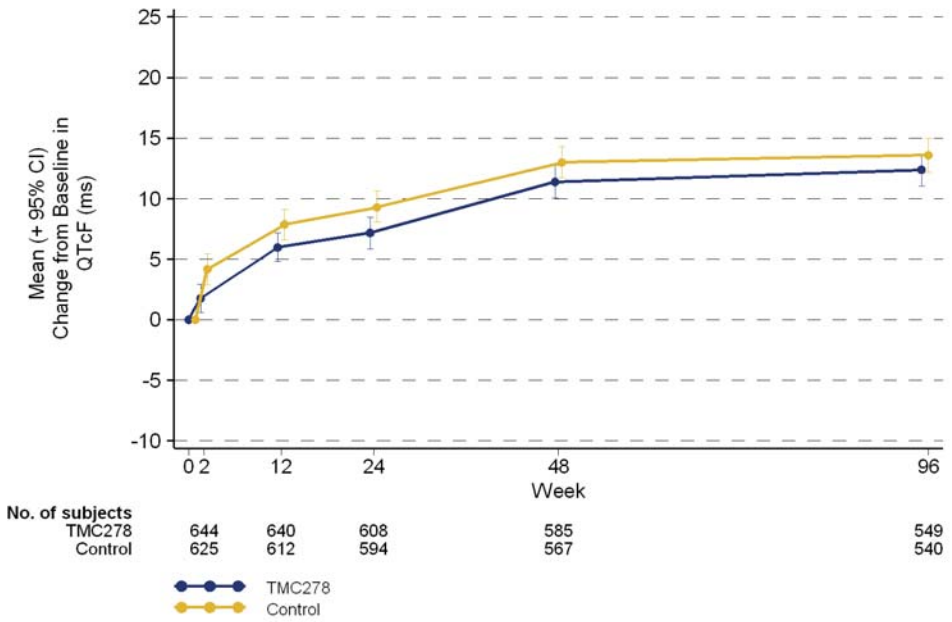
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.5, TMC278-C215-W96-Anal-Saf-AE/Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.7 and Display GEN.13.

Prolonged ECG QT was reported in 0.3% (2 subjects) in the RPV group and 1.8% in the control group.

2.1.9.5.2.1.1.2. QTc Over Time

Figure 17 presents the mean change from baseline in QTcF over time.

**Figure 17. RPV Studies C209 and C215: Mean Change from Baseline in QTcF Over Time (Phase 3 Week 96 Pooled Analysis)**

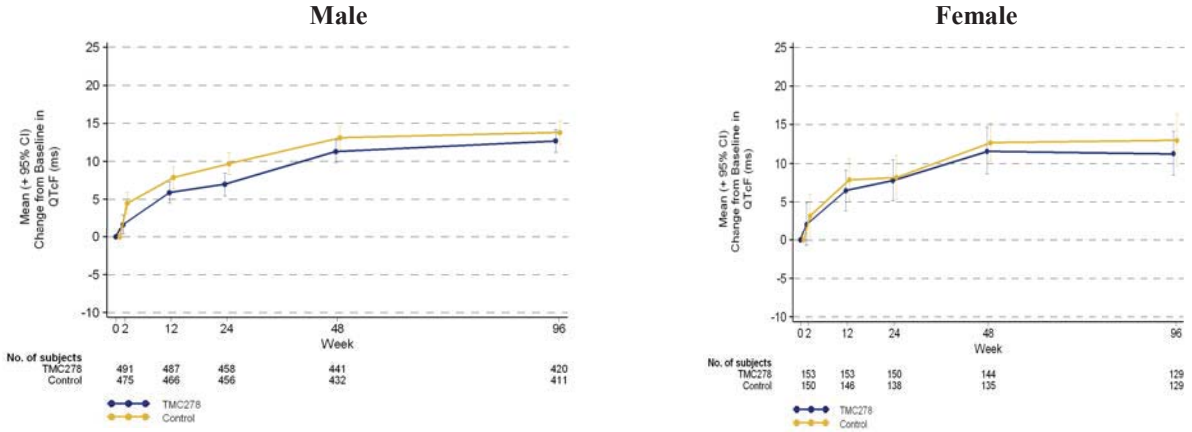



Source: TMC278-C904-W96-Anal-Saf-ECG/Display SAF.55.

The mean increase from baseline in QTcF was similar in both treatment groups at all timepoints and the mean change from baseline between Week 48 and Week 96 was relatively stable. At Week 96, the mean increase from baseline was 12.4 ms in the RPV group and 13.6 ms in the control group.

Figure 18 presents the mean change from baseline in QTcF over time by gender.

**Figure 18. RPV Studies C209 and C215: Mean Change from Baseline in QTcF Over Time by Gender: Male (Left); Female (Right) (Phase 3 Week 96 Pooled Analysis)**



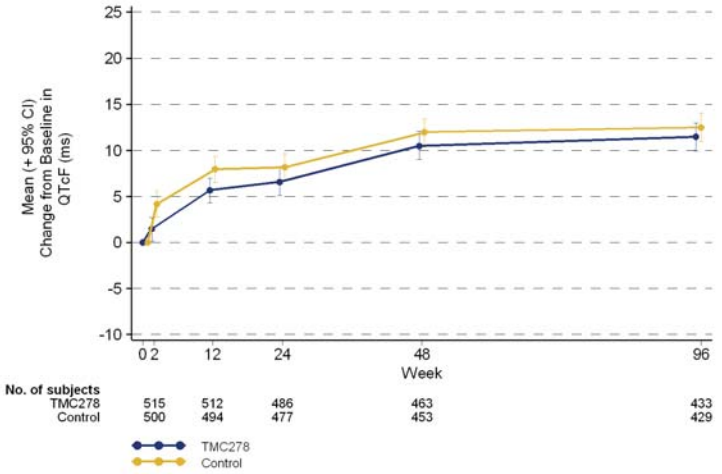

Source: TMC278-C904-W96-Anal-Saf-ECG/Display SAF.56.

The pattern of mean change from baseline over the 96-week treatment period was similar to that in the overall population for both male and female subjects. The subgroup analysis by race did not show any relevant differences in mean changes from baseline in QTcF between the different racial subgroups. In the subgroup analysis race-by-gender, the baseline QTcF and the increase from baseline over the 96-week treatment period was similar in Black/African American male and female subjects compared with White male and female subjects (TMC278 C904-W96-Anal-Saf-ECG/Display SAF.56). The number of subjects in the Asian and "other" subgroups was considered too small to draw any relevant conclusion.

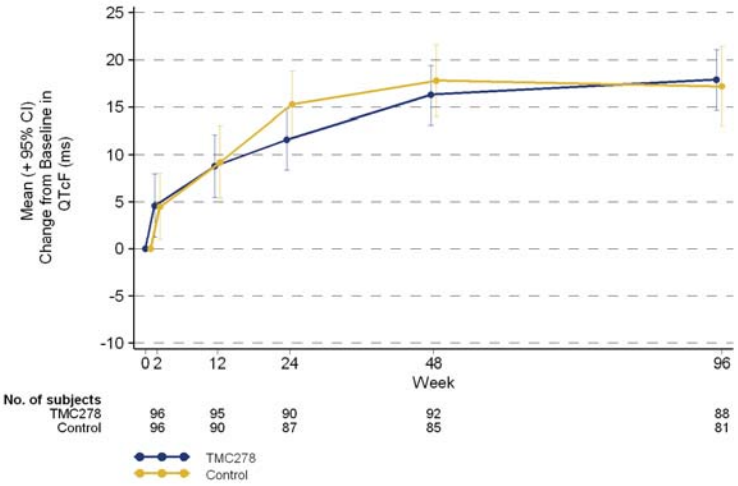
Figure 19 presents the mean change from baseline in QTcF over time by background N(t)RTI regimen.

**Figure 19.** **RPV Studies C209 and C215: Mean Change from Baseline in QTcF Over Time by Background N(t)RTI Regimen: FTC/TDF (Top); AZT/3TC (Middle); ABC/3TC (Bottom) (Phase 3 Week 96 Pooled Analysis)**

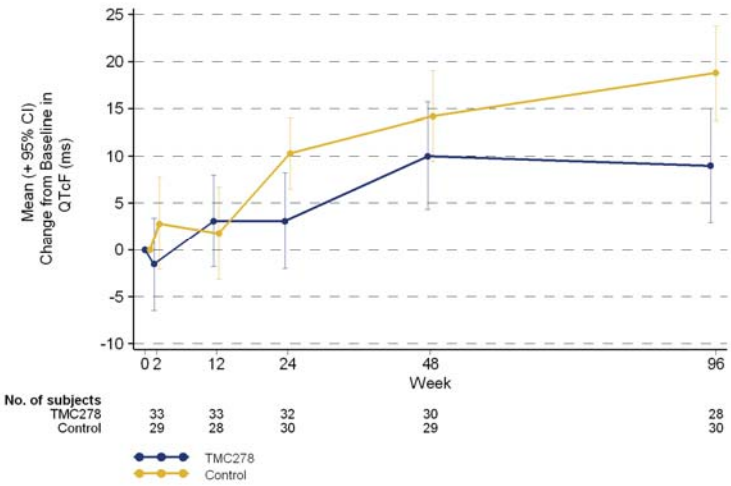
**FTC/TDF**




**AZT/3TC**




**ABC/3TC**




Source: TMC278-C904-W96-Anal-Saf-ECG/Display SAF.56.

The QTcF increase from baseline was lower in the FTC/TDF subgroup than in the AZT/3TC subgroup, with a QTcF increase at Week 96 of 11.5 ms in the RPV group and 12.5 ms in the control group (FTC/TDF) and 17.9 ms in the RPV group and 17.2 ms in the control group (AZT/3TC). In each of the background N(t)RTI regimen subgroups, the mean QTcF increase from baseline was similar in the 2 treatment groups (Figure 19).

Descriptive statistics of the mean maximum change from baseline in QTcF are presented in Table 62 for the overall population, and by comedication with a potential impact on QT interval. The mean maximum change from baseline in QTcF was calculated when subjects were taking (1) a cytochrome (CYP)3A4 inhibitor, (2) a potassium-depleting diuretic, (3) a drug with known potential QT-prolonging effect, or (4) no comedication with potential impact on QT interval. The number of subjects taking a potassium-depleting diuretic or a drug with known potential QT-prolonging effect was too small (10 subjects or fewer) to draw valid conclusions and these data are not presented in Table 62.

**Table 62. RPV Studies C209 and C215: Mean Baseline QTcF and Mean Maximum Change from Baseline in QTcF by Specific Subgroup of Comedication (Phase 3 Week 96 Pooled Analysis)**

| | C209 | | | | C215 | | | | Pooled | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RPV N = 346 | | Control N = 344 | | RPV N = 340 | | Control N = 338 | | RPV N = 686 | | Control N = 682 | |
| QTcF (ms) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) |
| **Overall** | | | | | | | | | | | | |
| At baseline | 344 | 389.7 (387.74; 391.66) | 338 | 387.9 (385.85; 389.98) | 338 | 387.8 (385.90; 389.72) | 321 | 389.2 (386.96; 391.37) | 682 | 388.8 (387.40; 390.13) | 659 | 388.5 (387.02; 390.03) |
| Mean maximum change from baseline | 344 | 19.9 (18.19; 21.62) | 338 | 21.6 (20.03; 23.26) | 338 | 23.3 (21.68; 24.84) | 321 | 23.4 (21.68; 25.06) | 682 | 21.6 (20.39; 22.74) | 659 | 22.5 (21.32; 23.65) |
| **Subjects with no use of comedication predisposing to QT interval prolongation[a]** | | | | | | | | | | | | |
| At baseline | 333 | 389.5 (387.57; 391.53) | 318 | 387.3 (385.21; 389.48) | 326 | 387.6 (385.66; 389.55) | 311 | 389.2 (386.92; 391.42) | 659 | 388.6 (387.20; 389.97) | 629 | 388.2 (386.70; 389.79) |
| Mean maximum change from baseline | 333 | 19.4 (17.68; 21.15) | 318 | 21.3 (19.70; 22.97) | 326 | 23.0 (21.42; 24.66) | 311 | 23.6 (21.91; 25.29) | 659 | 21.2 (20.02; 22.40) | 629 | 22.5 (21.28; 23.63) |
| **Subjects with concomitant use of CYP3A4 inhibitors[a]** | | | | | | | | | | | | |
| At baseline | 18 | 382.1 (377.06; 387.05) | 26 | 390.9 (383.28; 398.49) | 18 | 389.4 (381.05; 397.73) | 21 | 383.8 (373.69; 393.93) | 36 | 385.7 (380.94; 390.50) | 47 | 387.7 (381.70; 393.74) |
| Mean maximum change from baseline | 18 | 16.4 (7.52; 25.26) | 26 | 13.7 (6.14; 21.25) | 18 | 19.9 (11.81; 28.08) | 21 | 11.5 (3.40; 19.55) | 36 | 18.2 (12.43; 23.91) | 47 | 12.7 (7.38; 18.02) |

Two subgroups (potassium-depleting diuretics and other drugs with known QT-prolonging effect) were omitted from this table due to the small number of subjects in these subgroups.[a] A subject can be assigned to more than 1 subgroup.
Source: TMC278-C209-W96-Anal-Saf-ECG/Display SAF.41, TMC278-C215-W96-Anal-Saf-ECG/Display SAF.43 and TMC278-C904-W96-Anal-Saf-ECG/Display SAF.57.

In the RPV group, the mean maximum change from baseline was similar in the subgroup of subjects taking CYP3A4 inhibitors and in the subgroup of subjects without comedication with potential impact on QT interval.

#### 2.1.9.5.2.1.1.3. Other ECG Parameters Over Time

Small mean changes from baseline were observed in heart rate (HR), PR and QRS interval over the 96-week treatment period. There were no consistent changes over time in these parameters in the overall analysis and in any of the subgroup analyses (by background N[t]RTI regimen, by race, by gender, and race-by-gender) (TMC278-C904-W96-Anal-Saf-ECG/Display SAF.55 and Display SAF.56).

#### 2.1.9.5.2.1.1.4. ECG Abnormalities

A summary of the incidence of ECG abnormalities (worst abnormality) is presented in Table 63. The incidence of QTc abnormalities is presented by gender in Table 64.

**Table 63. RPV Studies C209 and C215: Treatment-Emergent ECG Abnormalities (Worst Case) Overall (Phase 3 Week 96 Analysis)**

| ECG parameter Abnormality, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **HR (bpm), N'** | **345** | **338** | **340** | **323** | **685** | **661** |
| Abnormally low | 38 (11.0) | 21 (6.2) | 28 (8.2) | 18 (5.6) | 66 (9.6) | 39 (5.9) |
| Abnormally high | 0 | 1 (0.3) | 2 (0.6) | 0 | 2 (0.3) | 1 (0.2) |
| **PR (ms), N'** | **345** | **338** | **340** | **323** | **685** | **661** |
| Abnormally high | 8 (2.3) | 9 (2.7) | 3 (0.9) | 7 (2.2) | 11 (1.6) | 16 (2.4) |
| **QRS (ms), N'** | **345** | **338** | **340** | **323** | **685** | **661** |
| Abnormally high | 2 (0.6) | 0 | 1 (0.3) | 0 | 3 (0.4) | 0 |
| **QTcF (ms), N'** | **345** | **338** | **340** | **323** | **685** | **661** |
| ]450 ms, 480 ms] | 4 (1.2) | 2 (0.6) | 10 (2.9) | 18 (5.6) | 14 (2.0) | 20 (3.0) |
| ]480 ms, 500 ms] | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 2 (0.3) | 2 (0.3) |
| **QTcF (ms), N'** | **344** | **338** | **338** | **321** | **682** | **659** |
| Increase by [30, 60] ms | 79 (23.0) | 84 (24.9) | 100 (29.6) | 92 (28.7) | 179 (26.2) | 176 (26.7) |
| Increase by > 60 ms | 5 (1.5) | 6 (1.8) | 5 (1.5) | 7 (2.2) | 10 (1.5) | 13 (2.0) |
| **QTcB (ms), N'** | **345** | **338** | **340** | **323** | **685** | **661** |
| ]450 ms, 480 ms] | 26 (7.5) | 25 (7.4) | 30 (8.8) | 40 (12.4) | 56 (8.2) | 65 (9.8) |
| ]480 ms, 500 ms] | 1 (0.3) | 3 (0.9) | 3 (0.9) | 8 (2.5) | 4 (0.6) | 11 (1.7) |
| > 500 ms | 0 | 0 | 1 (0.3) | 2 (0.6) | 1 (0.1) | 2 (0.3) |
| **QTcB (ms), N'** | **344** | **338** | **338** | **321** | **682** | **659** |
| Increase by [30, 60] ms | 100 (29.1) | 113 (33.4) | 115 (34.0) | 110 (34.3) | 215 (31.5) | 223 (33.8) |
| Increase by > 60 ms | 8 (2.3) | 15 (4.4) | 14 (4.1) | 19 (5.9) | 22 (3.2) | 34 (5.2) |

Note: Abnormally low HR was defined as ≤ 50 bpm and abnormally high HR was defined as ≥ 120 bpm. Abnormally high PR was defined as ≥ 210 ms.
Source: TMC278-C209-W96-Anal-Saf-ECG/Display SAF.42, TMC278-C215-W96-Anal-Saf-ECG/Display SAF.44 and Display SAF.46 and TMC278-C904-W96-Anal-Saf-ECG/Display SAF.58.

In both treatment groups, the most frequent ECG abnormalities were abnormally low HR (9.6% in the RPV group vs 5.9% in the control group) (this was the only ECG abnormality where the difference between treatment groups was > 3.5%), QTcB 450-480 ms (8.2% vs 9.8%, respectively), and abnormal increases from baseline in QTcF and QTcB (30-60 ms) (QTcF: 26.2% vs 26.7%, respectively, QTcB: 31.5% vs 33.8%, respectively). Abnormalities in QRS and PR were infrequent in both treatment groups.

There were no incidences of pathological QTcF (> 500 ms) in either treatment group.

Few subjects had an abnormal increase from baseline > 60 ms in QTcF; 1.5% of subjects in the RPV group and in 2.0% of subjects in the control group. An abnormal QTcF increase from baseline (≥ 30 ms) resulted in QTcF 480-500 ms in 0.1% (1 subject) in the RPV group. (TMC278-C904-W96-Anal-Saf-ECG/Display SAF.60).

**Table 64 RPV Studies C209 and C215: Treatment-Emergent ECG Abnormalities (Worst Case) by Gender (Phase 3 Week 96 Analysis)**

| ECG parameter Abnormality, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Female subjects** | | | | | | |
| **QTcF (ms), N'** | **78** | **68** | **90** | **92** | **168** | **160** |
| ]450 ms, 480 ms] | 2 (2.6) | 1 (1.5) | 5 (5.6) | 15 (16.3) | 7 (4.2) | 16 (10.0) |
| ]480 ms, 500 ms] | 0 | 1 (1.5) | 1 (1.1) | 0 | 1 (0.6) | 1 (0.6) |
| **QTcF (ms), N'** | **77** | **68** | **89** | **92** | **166** | **160** |
| Increase by [30, 60] ms | 14 (18.2) | 15 (22.1) | 29 (32.6) | 32 (34.8) | 43 (25.9) | 47 (29.4) |
| Increase by > 60 ms | 1 (1.3) | 1 (1.5) | 2 (2.2) | 2 (2.2) | 3 (1.8) | 3 (1.9) |
| **QTcB (ms), N'** | **78** | **68** | **90** | **92** | **168** | **160** |
| ]450 ms, 480 ms] | 18 (23.1) | 10 (14.7) | 17 (18.9) | 18 (19.6) | 35 (20.8) | 28 (17.5) |
| ]480 ms, 500 ms] | 0 | 1 (1.5) | 2 (2.2) | 7 (7.6) | 2 (1.2) | 8 (5.0) |
| > 500 ms | 0 | 0 | 1 (1.1) | 2 (2.2) | 1 (0.6) | 2 (1.3) |
| **QTcB (ms), N'** | **77** | **68** | **89** | **92** | **166** | **160** |
| Increase by [30, 60] ms | 21 (27.3) | 20 (29.4) | 34 (38.2) | 34 (37.0) | 55 (33.1) | 54 (33.8) |
| Increase by > 60 ms | 2 (2.6) | 2 (2.9) | 1 (1.1) | 7 (7.6) | 3 (1.8) | 9 (5.6) |
| **Male subjects** | | | | | | |
| **QTcF (ms), N'** | **267** | **270** | **250** | **231** | **517** | **501** |
| ]450 ms, 480 ms] | 2 (0.7) | 1 (0.4) | 5 (2.0) | 3 (1.3) | 7 (1.4) | 4 (0.8) |
| ]480 ms, 500 ms] | 1 (0.4) | 0 | 0 | 1 (0.4) | 1 (0.2) | 1 (0.2) |
| **QTcF (ms), N'** | **267** | **270** | **249** | **229** | **516** | **499** |
| Increase by [30, 60] ms | 65 (24.3) | 69 (25.6) | 71 (28.5) | 60 (26.2) | 136 (26.4) | 129 (25.9) |
| Increase by > 60 ms | 4 (1.5) | 5 (1.9) | 3 (1.2) | 5 (2.2) | 7 (1.4) | 10 (2.0) |
| **QTcB (ms), N'** | **267** | **270** | **250** | **231** | **517** | **501** |
| ]450 ms, 480 ms] | 8 (3.0) | 15 (5.6) | 13 (5.2) | 22 (9.5) | 21 (4.1) | 37 (7.4) |
| ]480 ms, 500 ms] | 1 (0.4) | 2 (0.7) | 1 (0.4) | 1 (0.4) | 2 (0.4) | 3 (0.6) |
| **QTcB (ms), N'** | **267** | **270** | **249** | **229** | **516** | **499** |
| Increase by [30, 60] ms | 79 (29.6) | 93 (34.4) | 81 (32.5) | 76 (33.2) | 160 (31.0) | 169 (33.9) |
| Increase by > 60 ms | 6 (2.2) | 13 (4.8) | 13 (5.2) | 12 (5.2) | 19 (3.7) | 25 (5.0) |

Note: Abnormally low HR was defined as ≤ 50 bpm and abnormally high HR was defined as ≥ 120 bpm. Abnormally high PR was defined as ≥ 210 ms.

Source: TMC278-C209-W96-Anal-Saf-ECG/Display SAF.42, TMC278-C215-W96-Anal-Saf-ECG/Display SAF.44 and Display SAF.46 and TMC278-C904-W96-Anal-Saf-ECG/Display SAF.58.

A higher proportion of female subjects than male subjects in both treatment groups were reported with borderline QTcF 450-480 ms. The incidence of prolonged QTcF 480-500 ms was similar in female subjects (0.6% [1 subject] in both treatment groups) and in male subjects (0.2% [1 subject] in both treatment groups). In female subjects, the incidence of borderline QTcF 450-480 ms differed between treatment groups (4.2% in the RPV group vs 10.0% in the control group), but in male subjects the incidence was similar (1.4% in the RPV group vs 0.8% in the control group).

The incidence of ECG abnormalities by background N(t)RTI regimen is presented in Table 65.

**Table 65. RPV Studies C209 and C215: Treatment-Emergent ECG Abnormalities (Worst Case) by Background N(t)RTI Regimen (Phase 3 Week 96 Pooled Analysis)**

| ECG parameter Abnormality, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **FTC/TDF** | | | | | | |
| **HR (bpm), N'** | **345** | **338** | **204** | **191** | **549** | **529** |
| Abnormally low | 38 (11.0) | 21 (6.2) | 15 (7.4) | 12 (6.3) | 53 (9.7) | 33 (6.2) |
| Abnormally high | 0 | 1 (0.3) | 1 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| **PR (ms), N'** | **345** | **338** | **204** | **191** | **549** | **529** |
| Abnormally high | 8 (2.3) | 9 (2.7) | 2 (1.0) | 6 (3.1) | 10 (1.8) | 15 (2.8) |
| **QRS (ms), N'** | **345** | **338** | **204** | **191** | **549** | **529** |
| Abnormally high | 2 (0.6) | 0 | 0 | 0 | 2 (0.4) | 0 |
| **QTcF (ms), N'** | **345** | **338** | **204** | **191** | **549** | **529** |
| ]450 ms, 480 ms] | 4 (1.2) | 2 (0.6) | 3 (1.5) | 5 (2.6) | 7 (1.3) | 7 (1.3) |
| ]480 ms, 500 ms] | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.2) | 1 (0.2) |
| **QTcF (ms), N'** | **344** | **338** | **203** | **190** | **547** | **528** |
| Increase by [30, 60] ms | 79 (23.0) | 84 (24.9) | 44 (21.7) | 50 (26.3) | 123 (22.5) | 134 (25.4) |
| Increase by > 60 ms | 5 (1.5) | 6 (1.8) | 3 (1.5) | 3 (1.6) | 8 (1.5) | 9 (1.7) |
| **QTcB (ms), N'** | **345** | **338** | **204** | **191** | **549** | **529** |
| ]450 ms, 480 ms] | 26 (7.5) | 25 (7.4) | 11 (5.4) | 16 (8.4) | 37 (6.7) | 41 (7.8) |
| ]480 ms, 500 ms] | 1 (0.3) | 3 (0.9) | 0 | 2 (1.0) | 1 (0.2) | 5 (0.9) |
| **QTcB (ms), N'** | **344** | **338** | **203** | **190** | **547** | **528** |
| Increase by [30, 60] ms | 100 (29.1) | 113 (33.4) | 51 (25.1) | 51 (26.8) | 151 (27.6) | 164 (31.1) |
| Increase by > 60 ms | 8 (2.3) | 15 (4.4) | 7 (3.4) | 8 (4.2) | 15 (2.7) | 23 (4.4) |

| ECG parameter Abnormality, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **AZT/3TC** | | | | | | |
| **HR (bpm), N'** | **-** | **-** | **101** | **99** | **101** | **99** |
| Abnormally low | - | - | 10 (9.9) | 1 (1.0) | 10 (9.9) | 1 (1.0) |
| Abnormally high | - | - | 1 (1.0) | 0 | 1 (1.0) | 0 |
| **PR (ms), N'** | **-** | **-** | **101** | **99** | **101** | **99** |
| Abnormally high | - | - | 1 (1.0) | 1 (1.0) | 1 (1.0) | 1 (1.0) |
| **QTcF (ms), N'** | **-** | **-** | **101** | **99** | **101** | **99** |
| ]450 ms, 480 ms] | - | - | 6 (5.9) | 11 (11.1) | 6 (5.9) | 11 (11.1) |
| ]480 ms, 500 ms] | - | - | 0 | 1 (1.0) | 0 | 1 (1.0) |
| **QTcF (ms), N'** | **-** | **-** | **100** | **98** | **100** | **98** |
| Increase by [30, 60] ms | - | - | 46 (46.0) | 34 (34.7) | 46 (46.0) | 34 (34.7) |
| Increase by > 60 ms | - | - | 1 (1.0) | 4 (4.1) | 1 (1.0) | 4 (4.1) |
| **QTcB (ms), N'** | **-** | **-** | **101** | **99** | **101** | **99** |
| ]450 ms, 480 ms] | - | - | 16 (15.8) | 20 (20.2) | 16 (15.8) | 20 (20.2) |
| ]480 ms, 500 ms] | - | - | 3 (3.0) | 5 (5.1) | 3 (3.0) | 5 (5.1) |
| > 500 ms | - | - | 0 | 2 (2.0) | 0 | 2 (2.0) |
| **QTcB (ms), N'** | **-** | **-** | **100** | **98** | **100** | **98** |
| Increase by [30, 60] ms | - | - | 52 (52.0) | 50 (51.0) | 52 (52.0) | 50 (51.0) |
| Increase by > 60 ms | - | - | 6 (6.0) | 9 (9.2) | 6 (6.0) | 9 (9.2) |
| **ABC/3TC** | | | | | | |
| **HR (bpm), N'** | **-** | **-** | **35** | **33** | **35** | **33** |
| Abnormally low | - | - | 3 (8.6) | 5 (15.2) | 3 (8.6) | 5 (15.2) |
| **QRS (ms), N'** | **-** | **-** | **35** | **33** | **35** | **33** |
| Abnormally high | - | - | 1 (2.9) | 0 | 1 (2.9) | 0 |
| **QTcF (ms), N'** | **-** | **-** | **35** | **33** | **35** | **33** |
| ]450 ms, 480 ms] | - | - | 1 (2.9) | 2 (6.1) | 1 (2.9) | 2 (6.1) |
| ]480 ms, 500 ms] | - | - | 1 (2.9) | 0 | 1 (2.9) | 0 |
| **QTcF (ms), N'** | **-** | **-** | **35** | **33** | **35** | **33** |
| Increase by [30, 60] ms | - | - | 10 (28.6) | 8 (24.2) | 10 (28.6) | 8 (24.2) |
| Increase by > 60 ms | - | - | 1 (2.9) | 0 | 1 (2.9) | 0 |

| ECG parameter<br>Abnormality, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV<br>N = 346 | Control<br>N = 344 | RPV<br>N = 340 | Control<br>N = 338 | RPV<br>N = 686 | Control<br>N = 682 |
| **QTcB (ms), N'** | **-** | **-** | **35** | **33** | **35** | **33** |
| ]450 ms, 480 ms] | - | - | 3 (8.6) | 4 (12.1) | 3 (8.6) | 4 (12.1) |
| ]480 ms, 500 ms] | - | - | 0 | 1 (3.0) | 0 | 1 (3.0) |
| > 500 ms | - | - | 1 (2.9) | 0 | 1 (2.9) | 0 |
| **QTcB (ms), N'** | **-** | **-** | **35** | **33** | **35** | **33** |
| Increase by [30, 60] ms | - | - | 12 (34.3) | 9 (27.3) | 12 (34.3) | 9 (27.3) |
| Increase by > 60 ms | - | - | 1 (2.9) | 2 (6.1) | 1 (2.9) | 2 (6.1) |

Note: Abnormally low HR was defined as ≤ 50 bpm and abnormally high HR was defined as ≥ 120 bpm. Abnormally high PR was defined as ≥ 210 ms.
Source: TMC278-C209-W96-Anal-Saf-ECG/Display SAF.42; TMC278-C215-W96-Anal-Saf-ECG/Display SAF.45; TMC278-C904-W96-Anal-Saf-ECG/Display SAF.52 and Display SAF.58.

The incidence of QTcF abnormalities and abnormal increases from baseline (≥ 30 ms) was higher in the AZT/3TC subgroup than in the FTC/TDF subgroup, both in the RPV group and in the control group. There was no difference between the RPV group and the control group with respect to the incidence of ECG abnormalities in any of the N(t)RTI subgroups, except in abnormally low HR in the FTC/TDF subgroup (9.7% vs 6.2%, respectively) and AZT/3TC subgroup (9.9% vs 1.0%, respectively) and borderline QTcF 450-480 ms in the AZT/3TC subgroup (5.9% vs 11.1%, respectively).

#### 2.1.9.5.2.1.1.5. Adverse Events Related to ECG

The incidence of ECG abnormality-related AEs are presented in Table 66.

**Table 66. RPV Studies C209 and C215: Treatment-Emergent ECG Abnormality-Related Adverse Events (Phase 3 Week 96 Pooled Analysis)**

| Grouped Term<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Rate and Rhythm Disorders** | **13 (3.8)** | **20 (5.8)** | **14 (4.1)** | **9 (2.7)** | **27 (3.9)** | **29 (4.3)** |
| Palpitations | 9 (2.6) | 5 (1.5) | 5 (1.5) | 2 (0.6) | 14 (2.0) | 7 (1.0) |
| Bradycardia | 4 (1.2) | 2 (0.6) | 2 (0.6) | 2 (0.6) | 6 (0.9) | 4 (0.6) |
| Sinus bradycardia | 0 | 2 (0.6) | 3 (0.9) | 0 | 3 (0.4) | 2 (0.3) |
| Supraventricular extrasystoles | 1 (0.3) | 0 | 1 (0.3) | 0 | 2 (0.3) | 0 |
| Heart rate irregular | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) | 0 |
| Atrial fibrillation | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| HR increased | 0 | 0 | 1 (0.3) | 1 (0.3) | 1 (0.1) | 1 (0.1) |
| Sinus arrhythmia | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| Tachycardia | 0 | 7 (2.0) | 1 (0.3) | 2 (0.6) | 1 (0.1) | 9 (1.3) |
| Atrial flutter | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Brugada syndrome | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |
| Extrasystoles | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Sinus tachycardia | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Supraventricular tachyarrhythmia | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Supraventricular tachycardia | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |
| Ventricular extrasystoles | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| **Conduction disorders** | **9 (2.6)** | **9 (2.6)** | **16 (4.7)** | **30 (8.9)** | **25 (3.6)** | **39 (5.7)** |
| Bundle branch block right | 2 (0.6) | 5 (1.5) | 7 (2.1) | 5 (1.5) | 9 (1.3) | 10 (1.5) |
| Conduction disorder | 4 (1.2) | 2 (0.6) | 2 (0.6) | 4 (1.2) | 6 (0.9) | 6 (0.9) |
| ECG T wave abnormal | 1 (0.3) | 1 (0.3) | 4 (1.2) | 5 (1.5) | 5 (0.7) | 6 (0.9) |
| Bundle branch block | 0 | 0 | 4 (1.2) | 4 (1.2) | 4 (0.6) | 4 (0.6) |
| ECG QT prolonged | 0 | 1 (0.3) | 2 (0.6) | 11 (3.3) | 2 (0.3) | 12 (1.8) |
| Atrioventricular block first degree | 1 (0.3) | 1 (0.3) | 0 | 2 (0.6) | 1 (0.1) | 3 (0.4) |
| Atrioventricular block second degree | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) | 0 |
| Bundle branch block left | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| ECG ST-T change | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| **Other** | **4 (1.2)** | **2 (0.6)** | **1 (0.3)** | **2 (0.6)** | **5 (0.7)** | **4 (0.6)** |
| ECG abnormal | 4 (1.2) | 2 (0.6) | 1 (0.3) | 1 (0.3) | 5 (0.7) | 3 (0.4) |
| ECG poor r-wave progression | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.18, TMC278-C215-W96-Anal-Saf-AE/Display SAF.18 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.29.

The most commonly reported ECG abnormality-related AEs in the RPV group were palpitations, reported in 2.0% subjects and 1.0% [7 subjects] in the control group, and right bundle branch block, reported in 1.3% [9 subjects] in the RPV group and 1.5% in the control group. All other ECG abnormality-related AEs were reported in < 1.0% in the RPV group.

Electrocardiogram abnormality-related SAEs, ECG abnormality-related AEs that led to discontinuation, and Grade 3 and 4 ECG abnormality-related AEs were rare.

2.1.9.5.2.2. ART Naive Adolescent Subjects

2.1.9.5.2.2.1. Study C213

Mean and median ECG values were visually inspected for trends over time; mean and median changes from baseline were generally small. None of the mean or median changes in ECG values were considered clinically relevant (TMC278-C213-W48- CSR/TSFECG02). No HR, PR interval or QRS interval abnormalities were observed (TMC278-C213-W48-CSR/TSFECG03).

None of the subjects had a grade 1 (pediatric) or borderline (adults) QTcF value (≥450 ms for pediatric and >450 ms for adults, ie >16 years). Increases in QTcF by 30 to 60 ms were observed in 3/36 (8.3%) subjects (Table 67).

No ECG-related AEs or clinically relevant ECG abnormalities were reported in this study.

**Table 67 RPV Study C213: Cross-Tabulation of the Worst QTc Increase From Baseline Versus Worst Abnormality of the Actual Value (Intent-to-Treat)**

| | n (%) | Worst abnormality of the actual value | | |
|---|---|---|---|---|
| | | Normal | Grade 1 | Borderline |
| Worst Increase From Baseline | | | | |
| QTc (Fridericia, msec) | 36 | 36 | | |
| Normal | 33 (91.7%) | 33 | | |
| Increase by 30-60 ms | 3 (8.3%) | 3 | | |

QTc adult: normal ≤ 450 < borderline ≤ 480 < prolonged ≤ 500 < pathologically prolonged
QTc pediatric: Grade 1: 450 ≤ QTc ≤ 464, Grade 2: 465 ≤ QTc ≤ 479, Grade 3: QTc ≥ 480
Source: TMC278-C213-W48-CSR/Table 44

2.1.9.5.3. Complera/Eviplera Studies

2.1.9.5.3.1. Virologically Suppressed Subjects

2.1.9.5.3.1.1. Study GS-US-264-0111

There were no clinically important changes in vital signs (including body weight and BMI), ECGs, or physical examination findings during Study GS-US-264-0111.

2.1.9.5.3.1.2. Study GS-US-264-0106

ECG data were not collected during this study.

2.1.9.5.4. FTC/RPV/TAF Studies

No subjects had any treatment emergent abnormal, clinically significant ECG findings in the Phase 1 Studies of FTC/RPV/TAF.

2.1.9.6. Thyroid Safety

Effects on the thyroid gland were noted in pre-clinical studies of E/C/F/TAF in rats, characterized by increased organ weight, hypertrophy of follicular epithelium, and reduced serum concentrations of T4. The effects occurred similarly in males and females and were noticed after 7 days of treatment. Upon longer duration of treatment, increased serum concentrations of TSH were recorded and also a differential effect on T3. TSH, T3, and T4 were assessed in the Phase 2 E/C/F/TAF Study GS-US-292-0102. No clinically relevant changes from baseline were observed for all 3 parameters, subsequently TSH, T3, and T4 were not assessed in the Phase 3 studies of E/C/F/TAF.

2.1.9.6.1. E/C/F/TAF Studies

2.1.9.6.1.1. ART-Naive Subjects

2.1.9.6.1.1.1. Study GS-US-292-0102

There were no clinically relevant changes from baseline or differences between the treatment groups in median values for TSH, T3, or T4 in either group during the randomized phase. There were no clinically relevant changes from baseline in median values for TSH, T3, or T4 for the E/C/F/TAF group through the extension phase (GS-US-292-0102 Week 96 CSR, Section 11.6.4).

2.1.9.6.1.2. Virologically Suppressed Subjects in E/C/F/TAF Studies

2.1.9.6.1.2.1. Study GS-US-292-0102 Open-Label Extension

There were no clinically relevant changes from baseline in median values for TSH, T3, or T4 in the switch groups (GS-US-292-0102 Week 96 CSR, Section 11.6.4).

2.1.9.7. Adrenal Safety

Based on the Week 48 analysis, all data related to adrenal safety from preclinical and clinical trials were assessed by an independent endocrinologist in order to determine the effect of RPV on steroidogenesis within the adrenal gland and the gonads. Specific adrenal toxicity monitoring was not included in the studies of FTC, TAF, or FTC/RPV/TDF. Therefore, adrenal safety data are presented below for RPV studies only.

Descriptive statistics of actual values and changes from baseline in basal values of cortisol, 17-hydroxy (OH) progesterone and aldosterone are displayed for trial C209 in TMC278-C209-W96-Anal-Saf-Endo/Display SAF.29 and Display SAF.30, for trial C215 in TMC278-C215-W96-Anal-Saf-Endo/Display SAF.30 and Display SAF.31, and for the Phase 3 Week 96 pooled analysis in TMC278-C904-W96-Anal-Saf-Endo/Display SAF.44 and Display SAF.45.

To determine whether there was an effect of RPV or control on the biosynthesis of adrenal and gonadal hormones in humans, basal cortisol, 17-OH-progesterone, aldosterone, androstenedione, dehydroepiandrosterone sulphate, progesterone and testosterone were assessed at specified timepoints before and during treatment. An ACTH stimulation test was also performed at baseline, at Weeks 48 and 96, and at unscheduled visits based on basal cortisol results or an abnormal ACTH stimulation test. During this stimulation test, cortisol, aldosterone, and 17-OH-progesterone values were assessed before (T0), and 30 (T30) and 60 (T60) minutes after ACTH administration.

Unless described, the results of the pooled Phase 3 trials and the individual trials C209 and C215 are similar. Similarities are not discussed.

2.1.9.7.1. RPV Studies

2.1.9.7.1.1. ART Naive Subjects

2.1.9.7.1.1.1. Studies C209 and C215

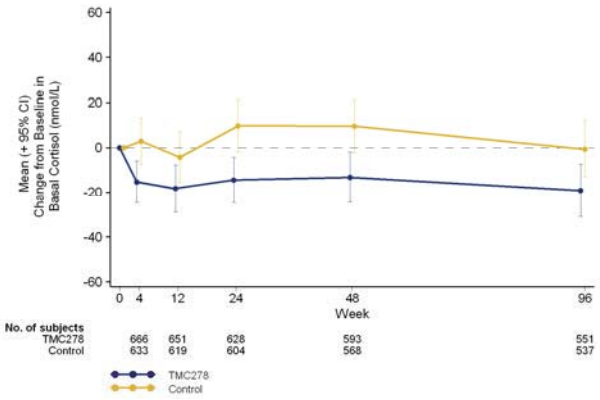
Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

2.1.9.7.1.1.1.1. Cortisol, 17-OH-Progesterone, Aldosterone and ACTH Stimulation Test

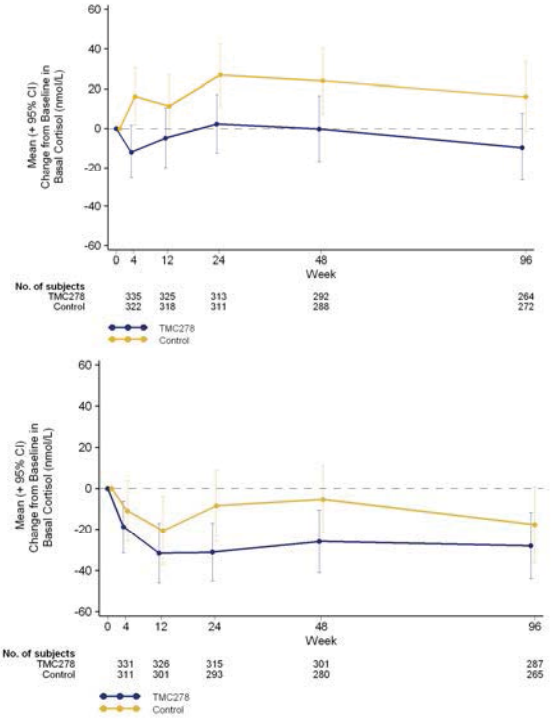
Figure 20 presents the mean change from baseline in basal cortisol over time.

**Figure 20. RPV Studies C209 and C215: Mean Change from Baseline in Basal (T0) Cortisol Over Time (Phase 3 Week 96 Pooled Analysis)**

**Pooled Phase 3 data**




**Trial C209** **Trial C215**




Source: TMC278-C209-W96-Anal-Saf-Endo/Display SAF.30, TMC278-C215-W96-Anal-Saf-Endo/Display SAF.31 and TMC278-C904-W96-Anal-Saf-Endo/Display SAF.45.

In the RPV group, mean values were below baseline throughout the 96-week treatment period with a maximum decrease at Week 12, after which values remained relatively stable. No notable change from baseline was observed in the control group. At Week 96, the overall mean change from baseline in basal cortisol level showed a decrease of 19.1 nmol/L in the RPV group, and an increase of 0.1 nmol/L in the control group (Table 68). The mean baseline basal (T0) cortisol levels in both treatment groups were lower in trial C209 than in trial C215. In trial C209, mean decreases from baseline in the RPV group were not observed at all timepoints and mean decreases were smaller than in trial C215. In the control group, the pattern of mean change from baseline differs between both C209 and C215 trials. In trial C209, there was a mean decrease from baseline in basal cortisol on RPV of 9.6 nmol/L and a mean increase of 16.9 nmol/L on control at Week 96. In trial C215, the mean decrease from baseline in basal cortisol was 27.9 nmol/L on RPV and 17.2 nmol/L on control at Week 96.

**Table 68. RPV Studies C209 and C215: Descriptive Statistics of Baseline Cortisol, 17-OH-Progesterone and Aldosterone and Change from Baseline at Weeks 48 and 96, Basal Values (T0) (Phase 3 Week 96 Pooled Analysis)**

| | C209 | | | | C215 | | | | Pooled | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RPV N = 346 | | Control N = 344 | | RPV N = 340 | | Control N = 338 | | RPV N = 686 | | Control N = 682 | |
| | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) |
| **Basal Cortisol (nmol/L)** | | | | | | | | | | | | |
| At baseline | 339 | 340.5 (328.39; 352.71) | 338 | 348.6 (335.23; 361.91) | 336 | 362.2 (348.85; 375.63) | 330 | 381.8 (367.69; 395.95) | 675 | 351.3 (342.29; 360.40) | 668 | 365.0 (355.23; 374.76) |
| Change from baseline at Week 48 | 292 | -0.1 (-16.68; 16.57) | 288 | 23.9 (7.09; 40.71) | 301 | -25.5 (-40.70; -10.31) | 280 | -5.4 (-22.02; 11.13) | 593 | -13.0 (-24.23; -1.71) | 568 | 9.4 (-2.40; 21.27) |
| Change from baseline at Week 96 | 264 | -9.6 (-26.69; 7.55) | 272 | 16.9 (-0.59; 34.45) | 287 | -27.9 (-44.08; -11.78) | 265 | -17.2 (-35.54; 1.13) | 551 | -19.1 (-30.87; -7.39) | 537 | 0.1 (-12.63; 12.80) |
| **Basal 17-OH-progesterone (nmol/L)** | | | | | | | | | | | | |
| At baseline | 340 | 6.2 (5.82; 6.66) | 336 | 6.3 (5.84; 6.68) | 332 | 6.2 (5.79; 6.58) | 327 | 6.1 (5.75; 6.50) | 672 | 6.2 (5.92; 6.50) | 663 | 6.2 (5.91; 6.47) |
| Change from baseline at Week 48 | 288 | 0.4 (-0.14; 0.87) | 282 | 0.4 (-0.02; 0.78) | 292 | 0.0 (-0.45; 0.47) | 277 | 0.4 (-0.11; 0.86) | 580 | 0.2 (-0.15; 0.53) | 559 | 0.4 (0.07; 0.69) |
| Change from baseline at Week 96 | 267 | 0.4 (-0.23; 0.96) | 268 | 0.5 (0.07; 0.98) | 278 | 0.5 (-0.26; 1.18) | 261 | 0.6 (0.05; 1.12) | 545 | 0.4 (-0.05; 0.88) | 529 | 0.6 (0.20; 0.90) |

| | C209 | | | | C215 | | | | Pooled | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RPV N = 346 | | Control N = 344 | | RPV N = 340 | | Control N = 338 | | RPV N = 686 | | Control N = 682 | |
| | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) | N' | Mean (95% CI) |
| **Basal Aldosterone (pmol/L)** | | | | | | | | | | | | |
| At baseline | 334 | 212.7 (195.85; 229.53) | 324 | 216.3 (198.04; 234.49) | 330 | 226.0 (207.90; 244.01) | 322 | 226.4 (208.02; 244.84) | 664 | 219.3 (206.96; 231.60) | 646 | 221.3 (208.41; 234.25) |
| Change from baseline at Week 48 | 277 | 23.4 (2.03; 44.67) | 267 | 10.3 (-15.68; 36.29) | 288 | 15.3 (-5.61; 36.22) | 265 | 4.4 (-18.39; 27.20) | 565 | 19.2 (4.36; 34.14) | 532 | 7.4 (-9.87; 24.61) |
| Change from baseline at Week 96 | 246 | 17.8 (-8.32; 43.85) | 250 | 8.0 (-15.91; 31.85) | 264 | 13.9 (-7.74; 35.48) | 243 | 1.4 (-21.52; 24.31) | 510 | 15.7 (-1.03; 32.53) | 493 | 4.7 (-11.77; 21.23) |

Source: TMC278-C209-W48-Anal-Saf-Endo/Display SAF.22 and Display SAF.23 and TMC278-C209-W96-Anal-Saf-Endo/Display SAF.30; TMC278-C215-W48-Anal-Saf-Endo/Display SAF.23 and Display SAF.24 and TMC278-C215-W96-Anal-Saf-Endo/Display SAF.33; TMC278-C904-W96-Anal-Saf-Endo/Display SAF.44 and Display SAF.45.

Small mean increases from baseline in 17-OH-progesterone levels were seen at Week 96 in both treatment groups (0.4 nmol/L and 0.6 nmol/L in RPV and control group). The mean increase from baseline in aldosterone at Week 96 was higher in the RPV group than in the control group (15.7 pmol/L and 4.7 pmol/L, respectively).

These adrenal findings indicate that neither RPV nor control had a clinically relevant inhibitory effect on 17-hydroxylase or 21-hydroxylase.

**ACTH Stimulation Test**

At Week 96, the mean change from baseline in maximum change in cortisol after ACTH stimulation was lower in the RPV group (+18.4 nmol/L) than in the control group (+54.1 nmol/L). Small mean increases from baseline in the maximum change in 17-OH-progesterone levels after ACTH stimulation (1.82 nmol/L and 2.63 nmol/L on RPV and control, respectively) and in aldosterone concentrations (17.7 pmol/L and 36.2 pmol/L on RPV and control, respectively) were observed.

2.1.9.7.1.1.1.2. Cortisol Abnormalities

The incidence of abnormal cortisol responses after ACTH stimulation is presented in Table 69.

**Table 69. RPV Studies C209 and C215: Treatment-Emergent Abnormal Cortisol Response to ACTH Stimulation (Worst Case) (Phase 3 Week 96 Pooled Analysis)**

| Parameter Abnormality, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Worst over time, N'** | **329** | **319** | **317** | **294** | **646** | **613** |
| Any abnormal ACTH test[a] | 28 (8.5) | 13 (4.1) | 26 (8.2) | 8 (2.7) | 54 (8.4) | 21 (3.4) |
| 450,500 | 13 (4.0) | 5 (1.6) | 14 (4.4) | 4 (1.3) | 27 (4.2) | 9 (1.5) |
| < 450 | 15 (4.6) | 8 (2.5) | 12 (3.8) | 4 (1.3) | 27 (4.2) | 12 (1.8) |
| **At least 2 consecutive ACTH tests[b]** | 280 (85.1) | 271 (85.0) | 297 (93.7) | 272 (92.6) | 577 (89.3) | 543 (88.6) |
| **At least 2 consecutive abnormal ACTH tests[c]** | 6 (2.1) | 1 (0.4) | 7 (2.4) | 1 (0.4) | 13 (2.3) | 2 (0.4) |
| **At least 2 consecutive abnormal ACTH tests and last test abnormal[c]** | 1 (0.4) | 1 (0.4) | 4 (1.3) | 1 (0.4) | 5 (0.9) | 2 (0.4) |

[b] Percentages based on the number of subjects with ACTH data during the 96-week treatment period
[c] Percentages based on the number of subjects with at least 2 ACTH tests during the 96-week treatment period.
Source: TMC278-C209-W96-Anal-Saf-Endo/Display SAF.33, TMC278-C215-W48-Anal-Saf-Endo/Display SAF.34 and TMC278-C904-W96-Anal-Saf-Endo/Display SAF.48.

The incidence of an abnormal cortisol response to ACTH stimulation was higher in the RPV group than the control group over the 96-week treatment period (8.4% vs 3.4%, respectively).

For the RPV group, 4.2% of subjects did not reach the lower threshold of 450 nmol/L compared to 1.8% in the control group.

The incidence of at least 2 consecutive abnormal cortisol responses (< 500 nmol/L) to ACTH stimulation was 2.3% in the RPV group compared to 0.4% [2 subjects] in the control group.

A subgroup analysis was planned and performed on the pooled Phase 3 trials of the ACTH stimulation test on subjects using ketoconazole or corticosteroids as concomitant medication. There were no subjects using ketoconazole concomitantly while an ACTH stimulation test was being performed in either treatment group in the individual trials C209 and C215.
Thirteen subjects in the RPV group and 10 subjects in the control group had an ACTH stimulation test while taking concomitant corticosteroids. These subject numbers are too small to draw relevant conclusions on a potential confounding effect of concomitant medication on the outcome of the ACTH stimulation test. Three of the 13 subjects in the RPV group with an ACTH stimulation test while taking corticosteroids had an abnormal cortisol response (< 500 nmol/L) to ACTH stimulation, compared to none of the 10 such subjects in the control group.

No endocrine events were reported as SAEs. No subjects discontinued the trial due to an AE of decreased blood cortisol (nor for any other endocrine event of interest). No Grade 3 and 4 endocrine AEs were reported.

There were no clinical signs or symptoms suggestive of an adrenal or gonadal dysfunction in either treatment group.

2.1.9.7.1.2. ART-Naive Adolescent Subjects

2.1.9.7.1.2.1. Study C213

2.1.9.7.1.2.1.1. Cortisol, 17-OH-Progesterone, Aldosterone and ACTH Stimulation Test

There were no consistent mean or median changes from baseline in basal cortisol levels over the first 48 weeks of treatment. At Week 48, a mean (SE) increase of 43.8 nmol/L (18.17) (median [range] increase of 36.0 nmol/L [-120; 296]) from baseline was reported.

There were no clinically relevant mean or median changes from baseline in basal or stimulated 17-hydroxyprogesterone and aldosterone levels (TMC278-C213-W48-CSR/TSFEN03).

The majority of subjects achieved ACTH stimulated cortisol values above the cut-off of 500 nmol/L. At Week 48, 4 subjects had a treatment-emergent abnormal ACTH stimulation test ≥450 - <500 nmol/L and 1 subject had a treatment-emergent abnormal ACTH stimulation test <450 nmol/L. One subject had an abnormal ACTH stimulation test <450 nmol/L at baseline, but achieved an ACTH stimulation test ≥500 nmol/L at Week 48 (Table 70). These changes were considered normal interindividual and intraindividual variability, as was also observed from the results of the scheduled and unscheduled ACTH stimulation tests during the study, ie worst ACTH results (TMC278-C213-W48-CSR/LSFEN01).

**Table 70 RPV Study C213: Cross-tabulation of ACTH Testing (Intent-to-Treat)**

| Cortisol | ACTH Response[a] | N | n (%) | Baseline ACTH Response | | |
|---|---|---|---|---|---|---|
| | | | | ≥500 nmol/L | [450, 500[ nmol/L | <450 nmol/L |
| Week 48 | ≥500 nmol/L | 29 | 22 (75.9%) | 19 | 2 | 1 |
| | [450, 500] nmol/L | | 6 (20.7%) | 4 | 2 | 0 |
| | <450 nmol/L | | 1 (3.4%) | 1 | 0 | 0 |
| Worst Over Time | ≥500 nmol/L | 36 | 25 (69.4%) | 24 | 1 | 0 |
| | [450, 500] nmol/L | | 7 (19.4%) | 4 | 2 | 1 |
| | <450 nmol/L | | 4 (11.1%) | 2 | 1 | 1 |

a The ACTH test result is categorized based on the maximum cortisol measurement at each analysis time point (predose, 0.5h, or 1h time points).
Source: TMC278-C213-W48-CSR/Table 38

Blood cortisol decreased was reported as a grade 1 AE in 7 (19.4%) subjects. The AE was considered possibly related to RPV in 3 (8.3%) subjects, doubtfully related to RPV in 2 (5.6%) subjects and doubtfully related to ARV regimen in 2 (5.6%) subjects by the investigator. At the Week 48 analysis cut-off date, the AE had resolved in all but one of these subjects, who also had an abnormal ACTH stimulation test since baseline (TMC278-C213-W48-CSR/Section 8.4.1).

No subjects discontinued the study due to an AE of blood cortisol decreased (nor for any other endocrine events of interest). No subject was reported with an AE of adrenal insufficiency.

2.1.9.8. Skin and Subcutaneous Tissue Disorders

Severe skin reactions have been reported during postapproval use of Complera/Eviplera. Data from RPV studies are summarized below.

2.1.9.8.1. Skin Events of Interest

2.1.9.8.1.1. RPV Studies

2.1.9.8.1.1.1. ART-Naive Subjects

2.1.9.8.1.1.1.1. Studies C209 and C215

Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

Skin events of interest for RPV Studies C209 and C215 are summarized in Table 71.

**Table 71. RPV Studies C209 and C215: Summary of Treatment-Emergent Skin Events of Interest (Phase 3 Week 96 Pooled Analysis)**

| AE summary | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any, n (%)** | 68 (19.7) | 108 (31.4) | 59 (17.4) | 101 (29.9) | 127 (18.5) | 209 (30.6) |
| Grade 1 | 53 (15.3) | 77 (22.4) | 43 (12.6) | 67 (19.8) | 96 (14.0) | 144 (21.1) |
| Grade 2 | 22 (6.4) | 44 (12.8) | 16 (4.7) | 40 (11.8) | 38 (5.5) | 84 (12.3) |
| Grade 3 | 2 (0.6) | 2 (0.6) | 0 | 4 (1.2) | 2 (0.3) | 6 (0.9) |
| **Time to onset of first treatment-emergent event [days]** | | | | | | |
| Number of events | 80 | 137 | 61 | 118 | 141 | 255 |
| Median (range) | 80.0 (1 - 696) | 17.0 (1 - 756) | 112.0 (1 - 829) | 13.5 (1 - 674) | 87.0 (1 - 829) | 15.0 (1 - 756) |
| **Duration [days]** | | | | | | |
| Number of events | 91 | 138 | 64 | 125 | 155 | 263 |
| Median (range) | 34.0 (1 - 777) | 15.0 (1 - 746) | 30.5 (1 - 816) | 15.0 (1 - 844) | 31.0 (1 - 816) | 15.0 (1 - 844) |
| **Treatment-related[a] AE, n (%)** | **15 (4.3)** | **58 (16.9)** | **17 (5.0)** | **47 (13.9)** | **32 (4.7)** | **105 (15.4)** |
| **Any SAE, n (%)** | **0** | **1 (0.3)** | **0** | **1 (0.3)** | **0** | **2 (0.3)** |
| **Leading to permanent discontinuation, n (%)** | **1 (0.3)** | **5 (1.5)** | **0** | **7 (2.1)** | **1 (0.1)** | **12 (1.8)** |
| **Leading to temporary discontinuation, n (%)** | **2 (0.6)** | **9 (2.6)** | **0** | **10 (3.0)** | **2 (0.3)** | **19 (2.8)** |

[a] Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.3, Display SAF.25, Display SAF.26, and Display GEN.13.

There were 127 subjects (18.5%) in the RPV group, and 209 subjects (30.6%) in the control group with skin events of interest, respectively).

Skin events of interest were reported at a lower incidence and with lower grades in the RPV group than in the control group and were reported as treatment-related for a smaller proportion of subjects in the RPV group (4.7%) than in the control group (15.4%). The median time to onset of skin events of interest was longer in the RPV group than the control group (87 and 15 days, respectively), as was the median duration of skin events of interest (31 and 15 days, respectively), despite similar ranges.

No skin events of interest were reported as SAEs in the RPV group in the Week 96 pooled analysis. However in the control group, 1 subject was reported with Grade 3 generalized rash,

which was considered very likely related to study medication and led to permanent discontinuation and 1 subject was reported with Grade 2 rash, which was considered possibly related to study medication. Both events were reported as SAEs.

Skin events of interest which led to permanent discontinuation were reported in 0.1% (1 subject) in the RPV group and 1.8% in the control group.

The incidence of skin events of interest is summarized in Table 72.

**Table 72. RPV Studies C209 and C215: Treatment-Emergent Skin Events of Interest (Regardless of Severity and Drug Relatedness) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], Median (Range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any skin event of interest, n (%)** | **68 (19.7)** | **108 (31.4)** | **59 (17.4)** | **101 (29.9)** | **127 (18.5)** | **209 (30.6)** |
| **Rash, n (%)** | **45 (13.0)** | **92 (26.7)** | **34 (10.0)** | **87 (25.7)** | **79 (11.5)** | **179 (26.2)** |
| Rash | 26 (7.5) | 43 (12.5) | 15 (4.4) | 50 (14.8) | 41 (6.0) | 93 (13.6) |
| Pruritus | 8 (2.3) | 17 (4.9) | 15 (4.4) | 17 (5.0) | 23 (3.4) | 34 (5.0) |
| Prurigo | 5 (1.4) | 0 | 1 (0.3) | 0 | 6 (0.9) | 0 |
| Rash papular | 4 (1.2) | 6 (1.7) | 0 | 6 (1.8) | 4 (0.6) | 12 (1.8) |
| Rash maculo-papular | 3 (0.9) | 7 (2.0) | 0 | 8 (2.4) | 3 (0.4) | 15 (2.2) |
| Rash pruritic | 3 (0.9) | 7 (2.0) | 1 (0.3) | 2 (0.6) | 4 (0.6) | 9 (1.3) |
| Erythema | 2 (0.6) | 5 (1.5) | 5 (1.5) | 4 (1.2) | 7 (1.0) | 9 (1.3) |
| Dermatitis allergic | 1 (0.3) | 4 (1.2) | 1 (0.3) | 2 (0.6) | 2 (0.3) | 6 (0.9) |
| Rash macular | 1 (0.3) | 6 (1.7) | 1 (0.3) | 2 (0.6) | 2 (0.3) | 8 (1.2) |
| Urticaria | 1 (0.3) | 2 (0.6) | 1 (0.3) | 4 (1.2) | 2 (0.3) | 6 (0.9) |
| Urticaria chronic | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) | 0 |
| Drug eruption | 0 | 3 (0.9) | 0 | 0 | 0 | 3 (0.4) |
| Exfoliative rash | 0 | 1 (0.3) | 0 | 1 (0.3) | 0 | 2 (0.3) |
| Face edema | 0 | 1 (0.3) | 0 | 1 (0.3) | 0 | 2 (0.3) |
| Rash erythematous | 0 | 3 (0.9) | 0 | 1 (0.3) | 0 | 4 (0.6) |
| Rash generalised | 0 | 7 (2.0) | 0 | 0 | 0 | 7 (1.0) |
| Rash morbilliform | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |
| Rash pustular | 0 | 1 (0.3) | 0 | 1 (0.3) | 0 | 2 (0.3) |
| Swelling face | 0 | 1 (0.3) | 0 | 2 (0.6) | 0 | 3 (0.4) |

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Dermatitis/Eczema** | **19 (5.5)** | **11 (3.2)** | **18 (5.3)** | **11 (3.3)** | **37 (5.4)** | **22 (3.2)** |
| Eczema | 10 (2.9) | 4 (1.2) | 5 (1.5) | 5 (1.5) | 15 (2.2) | 9 (1.3) |
| Seborrhoeic dermatitis | 7 (2.0) | 3 (0.9) | 6 (1.8) | 4 (1.2) | 13 (1.9) | 7 (1.0) |
| Dermatitis | 3 (0.9) | 5 (1.5) | 6 (1.8) | 2 (0.6) | 9 (1.3) | 7 (1.0) |
| Dermatitis atopic | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| **Other** | **15 (4.3)** | **10 (2.9)** | **6 (1.8)** | **4 (1.2)** | **21 (3.1)** | **14 (2.1)** |
| Skin exfoliation | 7 (2.0) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 8 (1.2) | 2 (0.3) |
| Blister | 2 (0.6) | 1 (0.3) | 0 | 0 | 2 (0.3) | 1 (0.1) |
| Lip ulceration | 2 (0.6) | 0 | 0 | 1 (0.3) | 2 (0.3) | 1 (0.1) |
| Photosensitivity reaction | 2 (0.6) | 5 (1.5) | 1 (0.3) | 0 | 3 (0.4) | 5 (0.7) |
| Lip blister | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.1) | 1 (0.1) |
| Seborrhoea | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 | 2 (0.3) | 1 (0.1) |
| Skin ulcer | 1 (0.3) | 0 | 1 (0.3) | 0 | 2 (0.3) | 0 |
| Eosinophilic pustular folliculitis | 0 | 0 | 1 (0.3) | 2 (0.6) | 1 (0.1) | 2 (0.3) |
| Infected skin ulcer | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Neurodermatitis | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| Penile ulceration | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| **Dermatitis Contact** | **1 (0.3)** | **3 (0.9)** | **1 (0.3)** | **5 (1.5)** | **2 (0.3)** | **8 (1.2)** |
| Dermatitis contact | 1 (0.3) | 3 (0.9) | 1 (0.3) | 5 (1.5) | 2 (0.3) | 8 (1.2) |
| **Edema** | **1 (0.3)** | **0** | **0** | **0** | **1 (0.1)** | **0** |
| Eye swelling | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) | 0 |
| **Rash Vesicular** | **0** | **0** | **1 (0.3)** | **0** | **1 (0.1)** | **0** |
| Rash vesicular | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.5, TMC278-C215-W96-Anal-Saf-AE/Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.7 and Display GEN.13.

The most common skin event of interest was rash (grouped term) in both the RPV and control group. Rash is discussed separately below. The incidence of other skin events of interest was low in both treatment groups. Dermatitis/eczema (grouped term) was reported in 5.4% of subjects in the RPV group and 3.2% of subjects in the control group.

### 2.1.9.8.2. Rash Events

Serious rash events have been reported with RPV containing regimens.

2.1.9.8.2.1. RPV Studies

2.1.9.8.2.1.1. ART-Naive Subjects

2.1.9.8.2.1.1.1. Studies C209 and C215

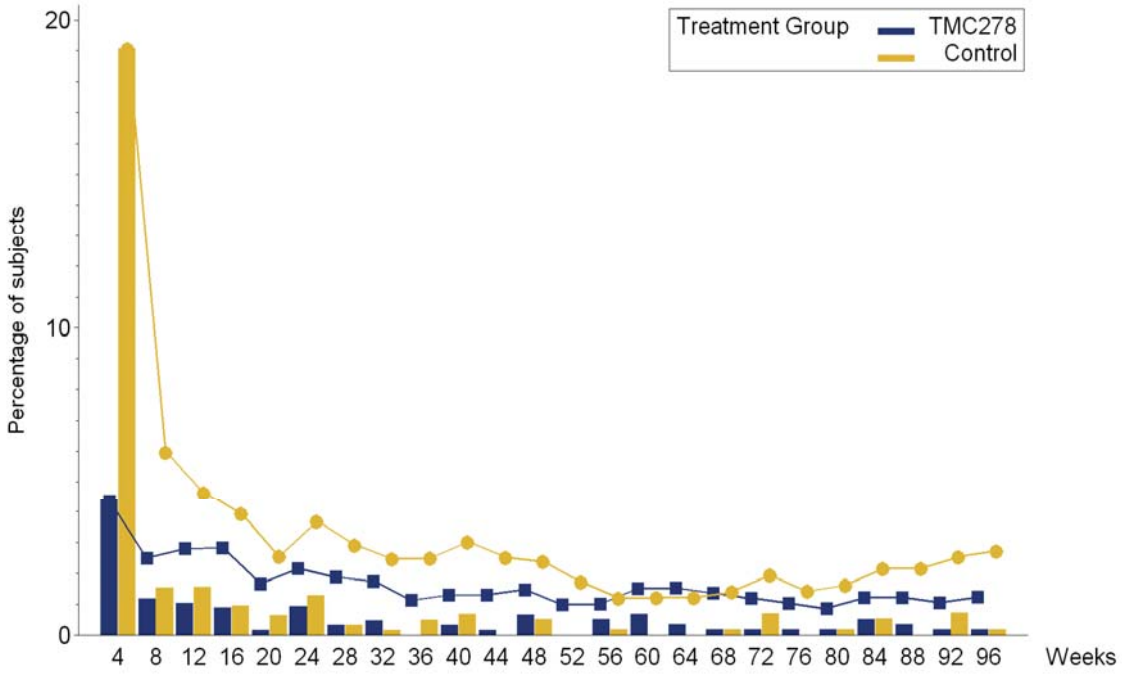
Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

In order to obtain a comprehensive overview of all reported types of rash, a grouped term including any type of rash was created and used in the analysis of rash.

The majority of the rash events in RPV subjects (regardless of drug relatedness) were Grade 1 or 2 in severity and there were no Grade 4 rash events.

The incidence and prevalence of rash events are displayed in Figure 21.

**Figure 21. RPV Studies C209 and C215: Incidence (Bars) and Prevalence (Lines) of Treatment-Emergent Rash (Grouped Term) Events Over Time (Phase 3 Week 96 Pooled Analysis)**




Source: TMC278-C904-W96-Anal-Saf-AE/Display SAF.30.

The incidence of rash events was highest in the first 4 weeks, with a much lower incidence in the RPV than the control group. Few new rash events occurred thereafter, and with comparable incidence in the RPV and control group. More rash events led to permanent discontinuation on

control than on RPV and the rest mostly resolved, therefore, the prevalence in the control group decreased after the first 4 weeks, but remained somewhat higher than on RPV during the first 48 weeks, after which the difference between treatment groups became less.

Treatment-related rash events are summarized in Table 73.

**Table 73. RPV Studies C209 and C215: Summary of Treatment-Emergent, Treatment-Related Rash (Grouped Term) Events (Phase 3 Week 96 Pooled Analysis)**

| AE summary | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any, n (%)** | **13 (3.8)** | **57 (16.6)** | **16 (4.7)** | **46 (13.6)** | **29 (4.2)** | **103 (15.1)** |
| Grade 1 | 9 (2.6) | 35 (10.2) | 13 (3.8) | 17 (5.0) | 22 (3.2) | 52 (7.6) |
| Grade 2 | 6 (1.7) | 26 (7.6) | 3 (0.9) | 29 (8.6) | 9 (1.3) | 55 (8.1) |
| Grade 3 | 1 (0.3) | 2 (0.6) | 0 | 3 (0.9) | 1 (0.1) | 5 (0.7) |
| **Time to onset of first treatment-emergent event [days]** | | | | | | |
| Number of events | 16 | 67 | 18 | 52 | 34 | 119 |
| Median (range) | 10.5 (1 - 407) | 11.0 (1 - 280) | 13.0 (1 - 502) | 10.5 (1 - 116) | 10.5 (1 - 502) | 11.0 (1 - 280) |
| **Duration [days]** | | | | | | |
| Number of events | 19 | 69 | 18 | 54 | 37 | 123 |
| Median (range) | 17.0 (3 - 281) | 10.0 (1 - 746) | 19.5 (2 - 605) | 10.0 (1 - 51) | 18.0 (2 - 605) | 10.0 (1 - 746) |
| **Any SAE, n (%)** | **0** | **1 (0.3)** | **0** | **0** | **0** | **1 (0.1)** |
| **Leading to permanent discontinuation, n (%)** | **1 (0.3)** | **4 (1.2)** | **0** | **7 (2.1)** | **1 (0.1)** | **11 (1.6)** |
| **Leading to temporary discontinuation, n (%)** | **1 (0.3)** | **8 (2.3)** | **0** | **8 (2.4)** | **1 (0.1)** | **16 (2.3)** |

'Treatment-related' was defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.3, Display SAF.25, Display SAF.26, and Display GEN.13.

There were 29 subjects (4.2%) in the RPV group and 103 subjects (15.1%) in the control group with rash events, respectively).

No treatment-related rash events were reported as SAEs in the RPV group. On control, 1 subject had Grade 3 generalized rash that was reported as an SAE.

Treatment-related rash events which led to permanent discontinuation was reported in 0.1% (1 subject) in the RPV group and 1.6% in the control group.

Treatment-related rash events were reported at a lower incidence and at a lower grade in the RPV group than in the control group. The difference in incidence was highly statistically significantly in favor of RPV ($p < 0.0001$; Fisher's Exact test; TMC278-C904-W96-Anal-Saf-AE/Display SAF.9). A similar pattern as in the pooled Phase 3 trials was seen in the incidence of treatment-related rash events in the individual trials C209 and C215, with a highly statistically significantly lower incidence on RPV than on control ($p < 0.0001$ for each trial; Fisher's Exact test; TMC278-C209-W96-Anal-Saf-AE/Display SAF.6 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.6).

The median time to onset of treatment-related rash events was similar in the RPV group and control group (10.5 and 11 days, respectively), while the median duration of treatment-related rash events was longer in the RPV group (18 days) than in the control group (10 days).

2.1.9.8.2.2. Complera/Eviplera Studies

2.1.9.8.2.2.1. Virologically Suppressed Subjects

2.1.9.8.2.2.1.1. Study GS-US-264-0111

Two subjects (4.1%) reported rash (PT) during the study. Grade 1 rash on left inner thigh that was considered related to study drug (onset, Day 3 and ongoing throughout the study) was reported in 1 subject. Grade 1 rash of the right axilla, considered unrelated to study drug, was reported in 1 subject.

2.1.9.8.2.2.1.2. Study GS-US-264-0106

Seven of 317 subjects (2.2%) in the FTC/RPV/TDF group and 4 of 152 subjects (2.6%) in the Delayed Switch group reported rash (PT) during the study. Two subjects (1.3%) remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study reported AEs of rash. All of these AEs of rash were considered to be nonserious and all but 2 of these AEs of rash were considered by the investigator to be unrelated to study drug.

- Subject [redacted] (Delayed Switch group) experienced a nonserious Grade 1 diffuse cutaneous rash that was considered related to study drug and resulted in temporary interruption of study drug (onset, Day 196 and ongoing at the time of the data cut-off for the Week 48 analysis).

- Subject [redacted] (FTC/RPV/TDF group) had a Grade 1 rash on the face that was considered to be related to study drug (onset, Day 62 and resolution, Day 78). This subject had a concurrent Grade 2 AE of pruritus (reported term: worsening of diffuse pruritis) that was also considered to be related to study drug (onset, Day 64 and resolution, Day 88). No action was taken with the study drug.

In addition to these AEs of rash (PT), erythematous rash (PT) was reported in 1 subject in the FTC/RPV/TDF group. Subject [redacted] had a Grade 1 erythematous rash on the anterior of the

neck that was considered related to study drug (onset, Day 28 and resolution, Day 59). No action was taken with the study drug due to this event.

2.1.9.9. Nervous System Disorders

Nervous system symptoms, including dizziness, are a known side effect of EFV {33968}, {33005}, the comparator in RPV Studies C209 and C215, therefore were evaluated as events of interest. Data from RPV are summarized below; nervous system disorders are not of special interest to FTC or TAF.

2.1.9.9.1. Neurologic Events

2.1.9.9.1.1. RPV Studies

2.1.9.9.1.1.1. ART-Naive Subjects

2.1.9.9.1.1.1.1. Studies C209 and C215

Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

Neurologic events of interest are summarized in Table 74.

**Table 74. RPV Studies C209 and C215: Summary of Treatment-Emergent Neurologic Events of Interest (Phase 3 Week 96 Pooled Analysis)**

| AE summary | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any, n (%)** | **85 (24.6)** | **150 (43.6)** | **110 (32.4)** | **168 (49.7)** | **195 (28.4)** | **318 (46.6)** |
| Missing | 2 (0.6) | 0 | 0 | 0 | 2 (0.3) | 0 |
| Grade 1 | 70 (20.2) | 123 (35.8) | 101 (29.7) | 135 (39.9) | 171 (24.9) | 258 (37.8) |
| Grade 2 | 20 (5.8) | 42 (12.2) | 14 (4.1) | 42 (12.4) | 34 (5.0) | 84 (12.3) |
| Grade 3 | 2 (0.6) | 4 (1.2) | 1 (0.3) | 4 (1.2) | 3 (0.4) | 8 (1.2) |
| Grade 4 | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.1) | 1 (0.1) |
| **Time to onset of first treatment-emergent event [days]** | | | | | | |
| Number of events | 105 | 197 | 119 | 216 | 224 | 413 |
| Median (range) | 6.0 (1 - 817) | 2.0 (1 - 819) | 7.0 (1 - 675) | 2.0 (1 - 506) | 6.5 (1 - 817) | 2.0 (1 - 819) |
| **Duration [days]** | | | | | | |
| Number of events | 109 | 210 | 133 | 231 | 242 | 441 |
| Median (range) | 15.0 (1 - 856) | 18.5 (1 - 918) | 11.0 (1 - 835) | 12.0 (1 - 901) | 13.0 (1 - 856) | 15.0 (1 - 918) |
| **Treatment-related[a] AE, n (%)** | **55 (15.9)** | **125 (36.3)** | **64 (18.8)** | **134 (39.6)** | **119 (17.3)** | **259 (38.0)** |
| **Any SAE, n (%)** | **1 (0.3)** | **1 (0.3)** | **1 (0.3)** | **0** | **2 (0.3)** | **1 (0.1)** |
| **Leading to permanent discontinuation, n (%)** | **1 (0.3)** | **4 (1.2)** | **0** | **2 (0.6)** | **1 (0.1)** | **6 (0.9)** |
| **Leading to temporary discontinuation, n (%)** | **1 (0.3)** | **4 (1.2)** | **1 (0.3)** | **1 (0.3)** | **2 (0.3)** | **5 (0.7)** |

[a] Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.3, Display SAF.25, Display SAF.26, and Display GEN.13.

There were 195 subjects [28.4%] in the RPV group and 318 subjects [46.6%] in the control group reported with neurologic events of interest in the Week 96 pooled analysis.

In the RPV group, SAEs of Grade 3 dizziness and Grade 4 alcohol poisoning were each reported in 1 subject. Both events were considered not related to study medication. In the control group, an SAE of Grade 4 dizziness was reported in 1 subject, which was considered possibly related to study medication. Neurologic events of interest which led to permanent discontinuation were reported in 0.1% (1 subject) in the RPV group and 0.9% (6 subjects) in the control group.

Neurologic events of interest were reported at a lower incidence and with lower grades in the RPV group than in the control group and were considered by the investigator to be treatment-related in a smaller proportion of subjects in the RPV group (17.3%) compared with the control group (38.0%). The difference in incidence was highly statistically significantly in favor of RPV, both for neurologic events of interest and for treatment-related neurologic events of interest ($p < 0.0001$; Fisher's Exact test; TMC278-C904-W96-Anal-Saf-AE/Display SAF.9). A similar pattern as in the pooled Phase 3 trials was seen in the incidence of (treatment-related) neurologic events of interest in the individual trials C209 and C215, with a highly statistically significantly lower incidence of neurologic events of interest and treatment-related neurologic events of interest on RPV than on control ($p < 0.0001$ for each trial; Fisher's Exact test; TMC278-C209-W96-Anal-Saf-AE/Display SAF.6 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.6).

The median time to onset for these events was 6.5 days in the RPV group and 2.0 days in the control group. The median duration was comparable between treatment groups (13 vs 15 days, respectively).

The incidence of neurologic events of interest is summarized in Table 75.

**Table 75. RPV Studies C209 and C215: Treatment-Emergent Neurologic Events of Interest (Regardless of Severity and Drug Relatedness) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], Median (Range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any neurologic event of interest** | **85 (24.6)** | **150 (43.6)** | **110 (32.4)** | **168 (49.7)** | **195 (28.4)** | **318 (46.6)** |
| **Nervous System Disorders** | **76 (22.0)** | **137 (39.8)** | **110 (32.4)** | **165 (48.8)** | **186 (27.1)** | **302 (44.3)** |
| Headache | 48 (13.9) | 43 (12.5) | 58 (17.1) | 53 (15.7) | 106 (15.5) | 96 (14.1) |
| Dizziness | 27 (7.8) | 91 (26.5) | 43 (12.6) | 111 (32.8) | 70 (10.2) | 202 (29.6) |
| Somnolence | 13 (3.8) | 23 (6.7) | 17 (5.0) | 28 (8.3) | 30 (4.4) | 51 (7.5) |
| Disturbance in attention | 2 (0.6) | 10 (2.9) | 5 (1.5) | 7 (2.1) | 7 (1.0) | 17 (2.5) |
| Amnesia | 1 (0.3) | 0 | 1 (0.3) | 2 (0.6) | 2 (0.3) | 2 (0.3) |
| Lethargy | 1 (0.3) | 4 (1.2) | 0 | 0 | 1 (0.1) | 4 (0.6) |
| Poor quality sleep | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 2 (0.3) | 2 (0.3) |
| Autonomic nervous system imbalance | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |
| Balance disorder | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.1) | 2 (0.3) |
| Depressed level of consciousness | 0 | 0 | 0 | 2 (0.6) | 0 | 2 (0.3) |
| Hypersomnia | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |
| Memory impairment | 0 | 2 (0.6) | 1 (0.3) | 1 (0.3) | 1 (0.1) | 3 (0.4) |
| Restless legs syndrome | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| **General Disorders and Administration Site Conditions** | **7 (2.0)** | **9 (2.6)** | **3 (0.9)** | **3 (0.9)** | **10 (1.5)** | **12 (1.8)** |
| Irritability | 7 (2.0) | 9 (2.6) | 3 (0.9) | 2 (0.6) | 10 (1.5) | 11 (1.6) |
| Sluggishness | 0 | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) |
| **Ear and Labyrinth Disorders** | **6 (1.7)** | **16 (4.7)** | **0** | **4 (1.2)** | **6 (0.9)** | **20 (2.9)** |
| Vertigo | 6 (1.7) | 16 (4.7) | 0 | 4 (1.2) | 6 (0.9) | 20 (2.9) |
| **Eye Disorders** | **4 (1.2)** | **5 (1.5)** | **0** | **4 (1.2)** | **4 (0.6)** | **9 (1.3)** |
| Vision blurred | 3 (0.9) | 4 (1.2) | 0 | 4 (1.2) | 3 (0.4) | 8 (1.2) |
| Visual disturbance | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.1) | 1 (0.1) |
| Photophobia | 0 | 2 (0.6) | 0 | 1 (0.3) | 0 | 3 (0.4) |
| **Injury, Poisoning, and Procedural Complications** | **1 (0.3)** | **0** | **0** | **1 (0.3)** | **1 (0.1)** | **1 (0.1)** |
| Alcohol poisoning | 1 (0.3) | 0 | 0 | 1 (0.3) | 1 (0.1) | 1 (0.1) |

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.5, TMC278-C215-W96-Anal-Saf-AE/Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.7 and Display GEN.13.

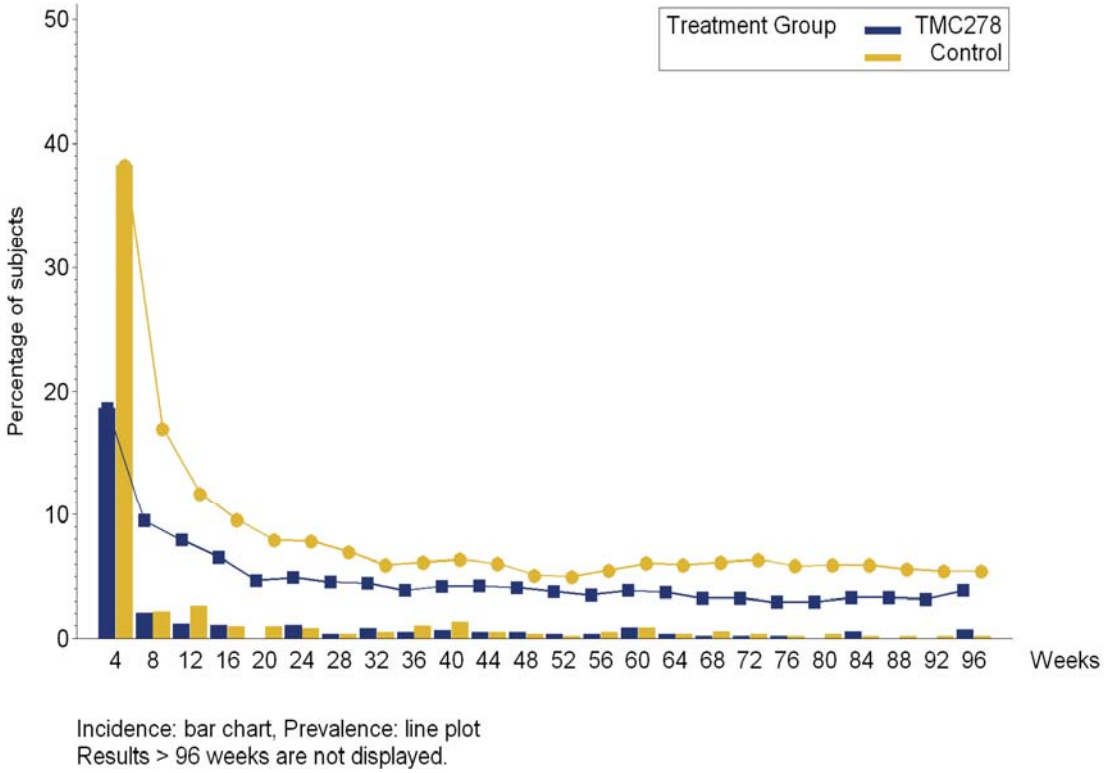
The most commonly reported neurologic events of interest on RPV were headache (15.5% in the RPV group vs 14.1% in the control group), dizziness (10.2% vs 29.6%, respectively), and somnolence (4.4% vs 7.5%, respectively). All other neurologic events of interest were reported in ≤ 1.5% of subjects in the RPV group.

The greatest differences in the incidence of neurologic events of interest between the RPV and control group were seen for dizziness (10.2% vs 29.6%, respectively) and somnolence (4.4% vs 7.5%, respectively), each reported at a lower incidence on RPV. The difference in the incidence of dizziness was highly statistically significant both for the pooled Phase 3 trials ($p < 0.0001$; Fisher's Exact test; TMC278-C904-W96-Anal-Saf-AE/Display SAF.9) and for individual trials C209 and C215 ($p < 0.0001$ for each trial; Fisher's Exact test; TMC278-C209-W96-Anal-Saf-AE/Display SAF.6 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.6) in favor of RPV. The difference in the incidence of somnolence between the treatment groups was not tested as the incidence in the overall population was less than 10%.

The incidence of neurologic events of interest was higher in RPV-treated subjects in trial C215 (32.4%) than in trial C209 (24.6%) and the 2 most common neurologic events of interest (headache and dizziness) were each reported at a higher incidence in trial C215 than in trial C209. There was no difference between the individual Phase 3 trials in the type of neurologic events of interest reported, with the exception of vertigo, which was reported at a higher incidence in trial C209 than in trial C215 both on RPV (1.7% vs no subjects, respectively) and control (4.7% vs 1.2% [4 subjects], respectively).

The incidence and prevalence of neurologic events of interest are displayed in Figure 22.

**Figure 22. RPV Studies C209 and C215: Incidence (Bars) and Prevalence (Lines) of Treatment-Emergent Neurologic Events of Interest Over Time (Phase 3 Week 96 Pooled Analysis)**




Source: TMC278-C904-W96-Anal-Saf-AE/Display SAF.30.

Neurologic events of interest emerged mainly in the first 4 weeks of treatment, when they were seen at approximately half the incidence in the RPV group than in the control group. The incidence and prevalence of neurologic events of interest decreased after 4-8 weeks, reached a plateau between Week 24 and Week 28, and remained at this level for the rest of the 96-week treatment period, with a somewhat higher prevalence in the control group.

**History of Neurologic and/or Psychiatric Illness**

TMC278-C904-Anal-Saf, Display SAF.6 summarizes the incidence of neurologic events of interest for subjects by previous history of neurologic or psychiatric illness, and by previous history of psychiatric illness only.

Neurologic events of interest were reported at a slightly greater incidence in subjects with a history of neurologic or psychiatric illness than in subjects with no history, both for TMC278 (34.5% versus 23.1%) and control (49.1% versus 43.4%).

The most common neurologic event of interest in the overall population, headache, was reported at a higher incidence in subjects with a history of neurologic or psychiatric illness than it was in subjects with no history of neurologic or psychiatric illness, both for TMC278 (18.4% versus

11.7%) and control (20.1% versus 10.5%). The next most common neurologic event of interest, dizziness, was seen at a similar incidence in subjects who did have a history of neurologic or psychiatric illness compared with those who did not, both for TMC278 (9.9% in both subgroups) and control (27.1% versus 29.1%, respectively).

2.1.9.10. Psychiatric Disorders

Depression is an important identified risk for RPV and the RPV component of Complera/Eviplera. Because serious psychiatric disorders have not been reported with use of FTC or TAF to date, only data from RPV studies are summarized below.

2.1.9.10.1. Psychiatric Events

2.1.9.10.1.1. RPV Studies

2.1.9.10.1.1.1. ART-Naive Subjects

2.1.9.10.1.1.1.1. Studies C209 and C215

Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

Psychiatric events of interest are summarized in Table 76.

**Table 76. RPV Studies C209 and C215: Summary of Treatment-Emergent Psychiatric Events of Interest (Phase 3 Week 96 Pooled Analysis)**

| AE summary | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any, n (%)** | **98 (28.3)** | **126 (36.6)** | **92 (27.1)** | **91 (26.9)** | **190 (27.7)** | **217 (31.8)** |
| Missing | 2 (0.6) | 0 | 0 | 1 (0.3) | 2 (0.3) | 1 (0.1) |
| Grade 1 | 67 (19.4) | 94 (27.3) | 64 (18.8) | 70 (20.7) | 131 (19.1) | 164 (24.0) |
| Grade 2 | 34 (9.8) | 45 (13.1) | 36 (10.6) | 34 (10.1) | 70 (10.2) | 79 (11.6) |
| Grade 3 | 9 (2.6) | 12 (3.5) | 3 (0.9) | 4 (1.2) | 12 (1.7) | 16 (2.3) |
| Grade 4 | 3 (0.9) | 1 (0.3) | 1 (0.3) | 0 | 4 (0.6) | 1 (0.1) |
| **Time to onset of first treatment-emergent event [days]** | | | | | | |
| Number of events | 137 | 174 | 111 | 134 | 248 | 308 |
| Median (range) | 70.0 (1 - 757) | 11.5 (1 - 803) | 38.0 (1 - 690) | 15.0 (1 - 716) | 57.0 (1 - 757) | 13.5 (1 - 803) |
| **Duration [days]** | | | | | | |
| Number of events | 132 | 181 | 110 | 139 | 242 | 320 |
| Median (range) | 81.0 (1 - 866) | 59.0 (1 - 950) | 86.0 (1 - 896) | 83.0 (1 - 908) | 85.0 (1 - 896) | 61.5 (1 - 950) |
| **Treatment-related[a] AE, n (%)** | **53 (15.3)** | **94 (27.3)** | **54 (15.9)** | **72 (21.3)** | **107 (15.6)** | **166 (24.3)** |
| **Any SAE, n (%)** | **6 (1.7)** | **6 (1.7)** | **3 (0.9)** | **3 (0.9)** | **9 (1.3)** | **9 (1.3)** |
| **Leading to permanent discontinuation, n (%)** | **5 (1.4)** | **9 (2.6)** | **6 (1.8)** | **6 (1.8)** | **11 (1.6)** | **15 (2.2)** |
| **Leading to temporary discontinuation, n (%)** | **2 (0.6)** | **3 (0.9)** | **2 (0.6)** | **2 (0.6)** | **4 (0.6)** | **5 (0.7)** |

[a] Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.3, Display SAF.25, Display SAF.26, and Display GEN.13.

There were 190 subjects [27.7%] in the RPV group and 217 subjects [31.8%] in the control group reported with psychiatric events of interest in the Week 96 pooled analysis.

Psychiatric events of interest were reported in 27.7% of subjects in the RPV group and 31.8% of subjects in the control group, and were reported at similar grades in both treatment groups. Psychiatric events of interest were reported to be treatment-related for a smaller proportion of subjects in the RPV group (15.6%) than in the control group (24.3%). In both treatment groups, 1.3% (9 subjects) had psychiatric events of interest that were reported as SAEs. In total,

1.6% and 2.2% of subjects in the RPV and control group, respectively, permanently discontinued due to psychiatric events of interest.

The difference in incidence of psychiatric events of interest was highly statistically significantly in favor of RPV for treatment-related psychiatric events of interest ($p < 0.0001$; Fisher's Exact test; TMC278-C904-W96-Anal-Saf-AE/Display SAF.9). A different pattern was seen in the individual trials C209 and C215: a statistically significant difference in the incidence of any psychiatric event of interest in favor of RPV was seen in trial C209 ($p = 0.0001$), but not in trial C215 ($p = 0.0758$).

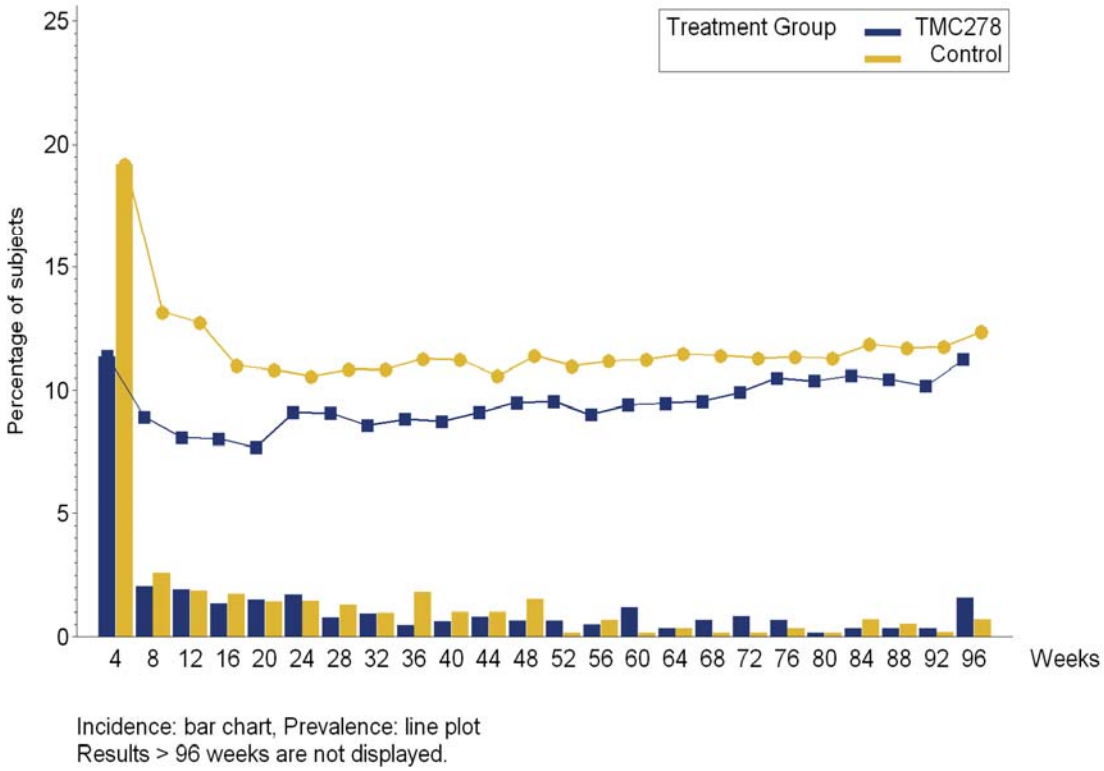
The median time to onset of psychiatric events of interest was longer in the RPV group (57 days) than in the control group (13.5 days). The median duration of these events was longer in the RPV group than in the control group (85 vs 61.5 days, respectively).

In general, a wide variety of different AEs were reported by small numbers of subjects in the SOC of psychiatric disorders. The most commonly reported psychiatric events of interest on RPV were insomnia (10.5% in the RPV group vs 8.5% in the control group), abnormal dreams (7.0% vs 9.8% , respectively), and depression (6.9% vs 6.0%, respectively).

As preplanned in the SAP, abnormal dreams/nightmares were grouped for the comparison of incidences because they belonged to the same medical concept. These AEs were reported at a lower incidence in the RPV group (8.9%) than in the control group (13.6%). The difference in incidence was statistically significantly ($p = 0.0061$; Fisher's Exact test; TMC278-C904-W96-Anal-Saf-AE/Display SAF.9) in favor of RPV. Although abnormal dreams/nightmares were also seen at a lower incidence in the RPV group than the control group in the individual trials C209 and C215, the difference between treatment groups was not statistically significant in trial C215. Anxiety was also seen at a lower incidence on RPV than on control (3.2% vs 6.0%, respectively) in the pooled Phase 3 trials, which was driven by the difference observed in trial C209 only (2.3% vs 7.8%, respectively).

The incidence and prevalence of psychiatric events of interest over time are displayed in Figure 23.

**Figure 23. RPV Studies C209 and C215: Incidence (Bars) and Prevalence (Lines) of Treatment-Emergent Psychiatric Events of Interest Over Time (Phase 3 Week 96 Pooled Analysis)**




Source: TMC278-C904-W96-Anal-Saf/Display SAF.30.

Psychiatric events of interest emerged mainly in the first 4 weeks of treatment, when they were seen at a higher incidence in the control group than in the RPV group. The prevalence of psychiatric events of interest remained relatively high over time and was somewhat lower in the RPV group compared with the control group.

**History of Neurologic and/or Psychiatric Illness**

TMC278-C904-Anal-Saf, Display SAF.6 summarizes the incidence of psychiatric events of interest for subjects by previous history of psychiatric illness only and by previous history of neurologic or psychiatric illness.

Psychiatric events of interest were reported in a greater proportion of subjects with a history of psychiatric illness than in subjects without a history of psychiatric illness, both for TMC278 (34.5% versus 21.1%) and control (41.0% versus 26.0%).

The most common psychiatric event of interest in the overall population, insomnia, was seen in a similar proportion of TMC278-treated subjects with a history of psychiatric illness than in TMC278-treated subjects with no history (6.3% versus 8.3%). In the control group, a somewhat greater proportion of subjects with a history of psychiatric illness reported insomnia (10.1%)

than subjects without a history of psychiatric illness (7.0%). The next most common psychiatric event of interest in the overall population, abnormal dreams, was seen at a higher incidence in subjects with a history of psychiatric illness than in subjects without a history of psychiatric illness, both for TMC278 (12.7% versus 5.1%) and control (12.9% versus 8.8%, respectively).

2.1.9.10.1.2. Complera/Eviplera Studies

2.1.9.10.1.2.1. Virologically Suppressed Subjects

2.1.9.10.1.2.1.1. Study GS-US-264-0111

In Study GS-US-264-0111, AEs in the psychiatric disorders SOC were reported in 14 subjects (28.6%), with the most frequently occurring AE in that SOC being insomnia (6 subjects [12.2%]). Depression was reported in 3 subjects (6.1%) (GS-US-264-0111, Section 11.2.4).

Three of 49 subjects (6.1%) reported AEs in the psychiatric disorders SOC that were considered by the investigator to be related to study drug. Depression was reported as a drug-related AE in 1 subject (2.0%).

No subject reported an SAE in the psychiatric disorders SOC.

2.1.9.10.1.2.1.2. Study GS-US-264-0106

Adverse events in the psychiatric disorders SOC were reported in 62 of 317 subjects (19.6%) in the FTC/RPV/TDF group, with the most frequently occurring AE in that SOC being insomnia (20 subjects [6.3%]). Depression was reported in 14 subjects (4.4%), depressed mood was reported in 3 subjects (0.9%) and suicidal ideation was reported in 1 subject (0.3%).

In the Delayed Switch group, 20 subjects (13.2%) reported AEs within the psychiatric disorders SOC, with the most frequently occurring AE in the psychiatric disorders SOC being insomnia (8 subjects [5.3%]). Depression was reported in 5 subjects (3.3%), and depressed mood and suicidal ideation were reported in 1 subject each (0.7%).

Of the 159 subjects remaining on their baseline ARV regimen during the first 24 weeks of the study (SBR group), 10 subjects (6.3%) reported AEs within the psychiatric disorders SOC. Depression was reported by 4 subjects (2.5%).

Nineteen of 317 subjects (6.0%) in the FTC/RPV/TDF group and 5 of 152 subjects (3.3%) in the Delayed Switch group reported AEs in the psychiatric disorders SOC that were considered by the investigator to be related to study drug. Of the AEs involving depression or suicide events, depression was reported as a drug-related AE in 2 subjects [0.6%] in the FTC/RPV/TDF group. There were no study drug-related AEs involving depression or suicide events in the Delayed Switch group and in subjects remaining on their baseline ARV regimen during the first 24 weeks of the study (SBR group).

Serious AEs in the psychiatric disorders SOC included suicidal ideation (1 subject each in the FTC/RPV/TDF and Delayed Switch groups), affective disorder (1 subject in the FTC/RPV/TDF

group), and bipolar disorder (1 subject in the FTC/RPV/TDF group). Suicidal ideation was reported by Subject [redacted] in the FTC/RPV/TDF group (onset, Day 157 and resolution, Day 159) and Subject [redacted] in the Delayed Switch group (onset, Day 307 and resolution, Day 334). Both of these SAEs of suicidal ideation resolved while study drug was ongoing. Subject [redacted] had a medical history of depression. None of the SAEs in the psychiatric disorders SOC were considered to be related to study drug. No subject reported an SAE in the psychiatric disorders SOC while remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study. Further details regarding the SAEs in the psychiatric disorders SOC are provided in GS-US-264-0106 Week 48 CSR, Section 11.2.4.

2.1.9.11. Hepatobiliary Disorders

Hepatocellular hypertrophy in mice and rats was associated with liver enzyme (i.e. UDP GT) induction and an increase of the organ weight following RPV.

Mild to moderate perivascular inflammatory reactions together with fibrosis and single hepatic cell necrosis in the central part of the lobules were seen in dogs and were associated with an increase in cholesterol, bilirubin, alkaline phosphatase and ALT. Moreover, mononuclear phagocytic system aggregates were noted and multifocal bile duct proliferation.

Hepatotoxicity was a key safety finding from nonclinical studies of RPV and was evaluated in clinical studies. Data from RPV studies are summarized below.

2.1.9.11.1. Hepatic Events

2.1.9.11.1.1. RPV Studies

2.1.9.11.1.1.1. ART-Naive Subjects

2.1.9.11.1.1.1.1. Studies C209 and C215

Results summarized in this section are based on the full Phase 3 Week 96 Pooled Analysis dataset as data for the FTC/TDF subset were not available.

Hepatic events of interest are summarized in Table 77.

**Table 77. RPV Studies C209 and C215: Summary of Treatment-Emergent Hepatic Events of Interest (Phase 3 Week 96 Pooled Analysis)**

| AE summary | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], median (range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any, n (%)** | **22 (6.4)** | **31 (9.0)** | **27 (7.9)** | **25 (7.4)** | **49 (7.1)** | **56 (8.2)** |
| Grade 1 | 14 (4.0) | 17 (4.9) | 8 (2.4) | 8 (2.4) | 22 (3.2) | 25 (3.7) |
| Grade 2 | 6 (1.7) | 8 (2.3) | 13 (3.8) | 9 (2.7) | 19 (2.8) | 17 (2.5) |
| Grade 3 | 4 (1.2) | 13 (3.8) | 11 (3.2) | 11 (3.3) | 15 (2.2) | 24 (3.5) |
| Grade 4 | 1 (0.3) | 2 (0.6) | 3 (0.9) | 5 (1.5) | 4 (0.6) | 7 (1.0) |
| **Time to onset of first treatment-emergent event [days]** | | | | | | |
| Number of events | 28 | 47 | 37 | 39 | 65 | 86 |
| Median (range) | 113.0 (15 - 731) | 168.0 (1 - 674) | 83.0 (1 - 673) | 85.0 (1 - 793) | 85.0 (1 - 731) | 110.0 (1 - 793) |
| **Duration [days]** | | | | | | |
| Number of events | 31 | 51 | 43 | 39 | 74 | 90 |
| Median (range) | 57.0 (10 - 707) | 58.0 (6 - 664) | 57.0 (8 - 832) | 58.0 (4 - 722) | 57.0 (8 - 832) | 58.0 (4 - 722) |
| **Treatment-related[a] AE, n (%)** | **5 (1.4)** | **13 (3.8)** | **9 (2.6)** | **5 (1.5)** | **14 (2.0)** | **18 (2.6)** |
| **Any SAE, n (%)** | **2 (0.6)** | **4 (1.2)** | **3 (0.9)** | **2 (0.6)** | **5 (0.7)** | **6 (0.9)** |
| **Leading to permanent discontinuation, n (%)** | **1 (0.3)** | **5 (1.5)** | **3 (0.9)** | **4 (1.2)** | **4 (0.6)** | **9 (1.3)** |
| **Leading to temporary discontinuation, n (%)** | **1 (0.3)** | **6 (1.7)** | **1 (0.3)** | **0** | **2 (0.3)** | **6 (0.9)** |

[a] Defined as possibly, probably, or very likely related to study medication in the opinion of the investigator.

Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C215-W96-Anal-Saf-AE/Display SAF.3, Display SAF.14 Part B, Display SAF.16 Part B, Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.3, Display SAF.25, Display SAF.26, and Display GEN.13.

There were 49 subjects [7.1%] in the RPV group and 56 subjects [8.2%] in the control group reported with hepatic events of interest in the Week 96 pooled analysis.

Overall, hepatic events of interest were reported to be treatment-related for 2.0% vs 2.6% of subjects, respectively. Graded hepatic events of interest were reported at a similar incidence in both treatment groups. The median time to onset of these hepatic events of interest was shorter in the RPV group than the control group (85 vs 110 days, respectively), but the median durations were comparable (57 vs 58 days, respectively). In the RPV group and control group, respectively, 0.7% (5 subjects) and 0.9% (6 subjects) had hepatic events of interest that were reported as SAEs. In total, 0.6% (4 subjects) and 1.3% (9 subjects) in the RPV and control group, respectively, permanently discontinued due to hepatic events of interest.

A comparison of AEs occurring in subjects with and without hepatitis B or C coinfection is provided in 5.1.10.2.

The incidence of hepatic events of interest is summarized in Table 78.

**Table 78. RPV Studies C209 and C215: Treatment-Emergent Hepatic Events of Interest (Regardless of Severity and Drug Relatedness) (Phase 3 Week 96 Pooled Analysis)**

| System Organ Class<br>Preferred term, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 340 | Control N = 338 | RPV N = 686 | Control N = 682 |
| **Treatment duration [weeks], Median (Range)** | **103.1 (0 - 135)** | **103.2 (1 - 136)** | **104.4 (2 - 133)** | **104.4 (0 - 133)** | **104.3 (0 - 135)** | **104.1 (0 - 136)** |
| **Any hepatic event of interest** | **22 (6.4)** | **31 (9.0)** | **27 (7.9)** | **25 (7.4)** | **49 (7.1)** | **56 (8.2)** |
| **Investigations** | **12 (3.5)** | **19 (5.5)** | **21 (6.2)** | **18 (5.3)** | **33 (4.8)** | **37 (5.4)** |
| AST increased | 7 (2.0) | 10 (2.9) | 10 (2.9) | 12 (3.6) | 17 (2.5) | 22 (3.2) |
| ALT increased | 6 (1.7) | 12 (3.5) | 8 (2.4) | 13 (3.8) | 14 (2.0) | 25 (3.7) |
| ALT abnormal | 2 (0.6) | 0 | 0 | 0 | 2 (0.3) | 0 |
| Blood bilirubin increased | 2 (0.6) | 0 | 5 (1.5) | 0 | 7 (1.0) | 0 |
| Liver function test abnormal | 1 (0.3) | 2 (0.6) | 1 (0.3) | 0 | 2 (0.3) | 2 (0.3) |
| Transaminases increased | 1 (0.3) | 4 (1.2) | 1 (0.3) | 1 (0.3) | 2 (0.3) | 5 (0.7) |
| Blood alkaline phosphatase increased | 0 | 2 (0.6) | 0 | 2 (0.6) | 0 | 4 (0.6) |
| Blood bilirubin unconjugated increased | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| Hepatic enzyme increased | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.1) | 2 (0.3) |
| **Hepatobiliary Disorders** | **8 (2.3)** | **13 (3.8)** | **7 (2.1)** | **8 (2.4)** | **15 (2.2)** | **21 (3.1)** |
| Cholelithiasis | 3 (0.9) | 2 (0.6) | 1 (0.3) | 2 (0.6) | 4 (0.6) | 4 (0.6) |
| Hepatic steatosis | 3 (0.9) | 3 (0.9) | 0 | 0 | 3 (0.4) | 3 (0.4) |
| Hepatomegaly | 1 (0.3) | 3 (0.9) | 1 (0.3) | 1 (0.3) | 2 (0.3) | 4 (0.6) |
| Hypertransaminasemia | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 2 (0.3) | 2 (0.3) |
| Cytolytic hepatitis | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Hepatic cirrhosis | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Hepatic function abnormal | 0 | 0 | 1 (0.3) | 3 (0.9) | 1 (0.1) | 3 (0.4) |
| Hepatitis | 0 | 0 | 1 (0.3) | 1 (0.3) | 1 (0.1) | 1 (0.1) |
| Hepatitis acute | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Hepatotoxicity | 0 | 0 | 1 (0.3) | 0 | 1 (0.1) | 0 |
| Hyperbilirubinemia | 0 | 1 (0.3) | 2 (0.6) | 0 | 2 (0.3) | 1 (0.1) |
| **Infections and Infestations** | **2 (0.6)** | **3 (0.9)** | **2 (0.6)** | **2 (0.6)** | **4 (0.6)** | **5 (0.7)** |
| Hepatitis C | 2 (0.6) | 2 (0.6) | 0 | 2 (0.6) | 2 (0.3) | 4 (0.6) |
| Hepatitis B | 0 | 1 (0.3) | 2 (0.6) | 0 | 2 (0.3) | 1 (0.1) |

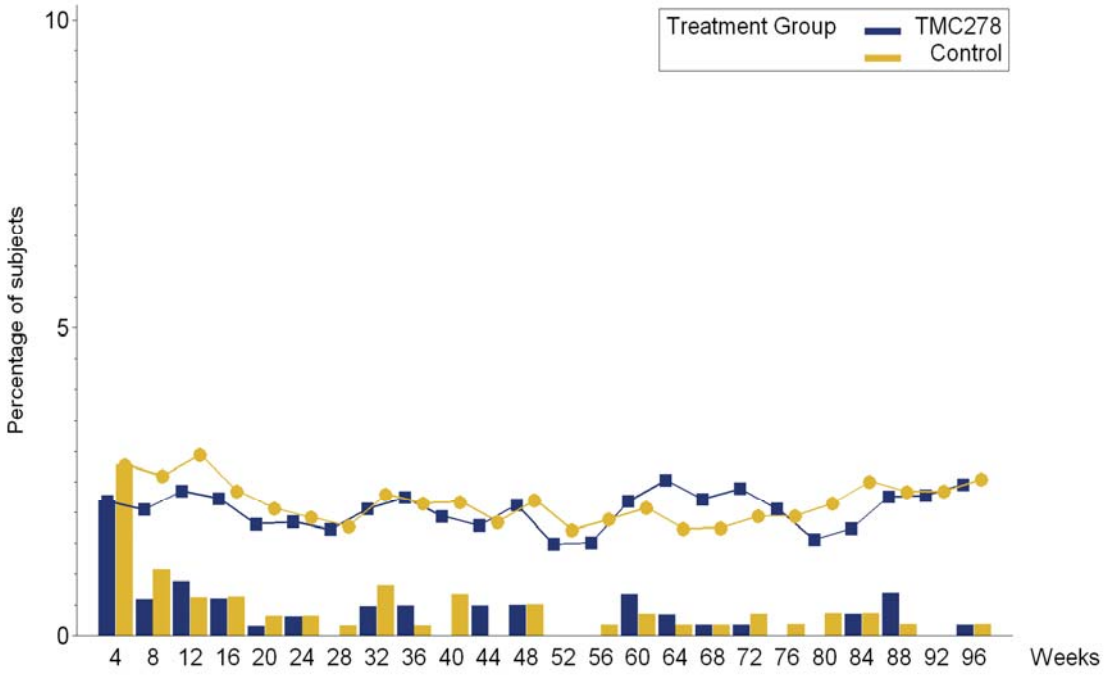
Source: TMC278-C209-W96-Anal-Saf-AE/Display SAF.5, TMC278-C215-W96-Anal-Saf-AE/Display GEN.13 and TMC278-C904-W96-Anal-Saf-AE/Display SAF.7 and Display GEN.13.

The most commonly reported hepatic events of interest in the RPV group were increased AST (2.5% in the RPV group vs 3.2% in the control group) and increased ALT (2.0% vs 3.7%,

respectively). All other hepatic events of interest were reported in ≤ 1% of subjects in the RPV group.

The incidence and prevalence of hepatic events of interest are displayed in Figure 24.

**Figure 24. RPV Studies C209 and C215: Incidence (Bars) and Prevalence (Lines) of Treatment-Emergent Hepatic Events of Interest Over Time (Phase 3 Week 96 Pooled Analysis)**




Source: TMC278-C904-W96-Anal-Saf/Display SAF.30.

The incidence of hepatic events of interest was low in both treatment groups, with the highest incidence seen in the first 4 weeks of treatment. The prevalence of hepatic events of interest was constant over time. Hepatic events of interest were seen at a similar incidence and prevalence in both treatment groups.

2.1.9.11.1.2. Complera/Eviplera Studies

2.1.9.11.1.2.1. Virologically Suppressed Subjects

2.1.9.11.1.2.1.1. Study GS-US-264-0111

No AEs in the hepatobiliary disorders SOC were reported during Study GS-US-264-0111. One AE of increased bilirubin was reported in the investigations SOC.

One subject ([redacted]) experienced increased bilirubin that was considered a Grade 2, treatment-related AE by the investigator. Baseline total bilirubin for this subject was 0.8 mg/dL. At the next study visit (Day 31), total bilirubin was 1.9 mg/dL (Grade 2). Bilirubin remained elevated throughout the remainder of the study, with a high of 2.6 mg/dL on Day 254 (Grade 2). Indirect bilirubin was also elevated starting on Day 31. No action was taken with regard to study drug, and the AE was ongoing at the time of study completion. No other AEs of liver-related laboratory abnormalities were reported during Study GS-US-264-0111.

2.1.9.11.1.2.1.2. Study GS-US-264-0106

Adverse events in the hepatobiliary disorders SOC were reported in 7 of 317 subjects (2.2%) in the FTC/RPV/TDF group. Hepatic steatosis and hypertransaminasaemia were reported in 2 subjects (0.6%) each in the FTC/RPV/TDF group. In the FTC/RPV/TDF group, all other AEs in the hepatobiliary disorders SOC were reported in 1 subject each. In the Delayed Switch group, the only AE reported in the hepatobiliary disorders SOC was cytolytic hepatitis (3 subjects [2.0%]). In addition, cytolysis (PT: cell death), associated with increase in transaminases, was reported in 5 subjects in the FTC/RPV/TDF group and 3 subjects in the Delayed Switch group. No subjects reported an AE in the hepatobiliary disorders SOC or the PT cell death while remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study.

One subject (0.3%) in the FTC/RPV/TDF group and 2 subjects (1.3%) in the Delayed Switch group reported AEs of cytolytic hepatitis that were considered by the investigator to be related to study drug. Four subjects (1.3%) in the FTC/RPV/TDF group and 3 subjects (2.0%) in the Delayed Switch group reported AEs of cell death (cytolysis) that were considered by the investigator to be related to study drug.

One SAE (cholecystitis) in the hepatobiliary disorders SOC was reported during the study. Subject [redacted] (FTC/RPV/TDF group) experienced an SAE of cholecystitis starting on Day 204, which was resolved by Day 207. This SAE was considered to be unrelated to study drug, and study drug was continued without interruption. No subjects reported an SAE in the hepatobiliary disorders SOC while remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study.

Adverse events of liver-related laboratory abnormalities (SOC: investigations) reported in the FTC/RPV/TDF group included the following: ALT increased in 4 subjects (1.3%), liver function test abnormal in 4 subjects (1.3%), AST increased in 2 subjects (0.6%), and transaminases increased, blood bilirubin increased, and hepatic enzyme increased in 1 subject (0.3%) each. In the Delayed Switch group, AEs of liver-related laboratory abnormalities included ALT increased in 4 subjects (2.6%), AST increased in 2 subjects (1.3%), transaminases increased in 2 subjects (1.3%), and liver function test abnormal and gamma-glutamyl transferase (GGT) increased in 1 subject (0.7%) each. In subjects remaining on their baseline ARV regimen (SBR group) during the first 24 weeks of the study, AEs of liver-related laboratory abnormalities included ALT increased and AST increased (1 subject [0.6%] each).

Study drug-related AEs of liver-related laboratory abnormalities reported in the FTC/RPV/TDF group included the following: ALT increased in 3 subjects (0.9%), liver function test abnormal in 4 subjects (1.3%), and AST increased and hepatic enzyme increased in 1 subject (0.3%) each. In

the Delayed Switch group, study drug-related AEs of liver-related laboratory abnormalities included ALT increased in 2 subjects (1.3%), transaminases increased in 2 subjects (1.3%), and liver function test abnormal and AST increased in 1 subject (0.7%) each. There were no study drug-related AEs of liver-related laboratory abnormalities reported in subjects remaining on their baseline ARV regimen during the first 24 weeks of the study.

No liver-related laboratory abnormalities were reported as SAEs during the study. Two subjects experienced AEs of liver-related laboratory abnormalities (transaminases increased [redacted]; ALT and AST increased [redacted]) resulting in permanent discontinuation of study drug; both in the Delayed Switch group. Subject [redacted] experienced a study drug-related AE of transaminases increased (Grade 2) on Day 194, resulting in permanent discontinuation of study drug. On Day 348, ALT and AST levels were within the normal range. This event was ongoing at the time of the data cut-off for the Week 48 analysis. Subject [redacted] experienced study drug-related AEs of ALT and AST increased (both Grade 3) on Day 275, resulting in permanent discontinuation of study drug. These events were considered to be resolved on Day 352.

## 2.2. Narratives

For the E/C/F/TAF studies, narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures, if applicable, are provided in the relevant CSRs. For the RPV studies, narratives for deaths, other SAEs (if at least possibly related to study medication), AEs leading to permanent discontinuation (if at least possibly related to study medication), Grade 3 or 4 AEs of interest, Grade 3 or 4 AEs in the SOC of renal and urinary disorders, skin exfoliation regardless of grade, renal failure regardless of grade, subjects with 2 consecutive abnormal ACTH stimulation tests, and subjects with a QTcF increase from screening >60 ms or actual QTcF value >500 ms, if applicable, are provided in the relevant CSRs. For the Complera/Eviplera studies, narratives for deaths, SAEs, discontinuations due to AEs, and overdose, if applicable, are provided in the relevant CSRs.

# 3. CLINICAL LABORATORY EVALUATIONS

In the following sections, a summary of the clinical laboratory evaluations relevant for the FTC/RPV/TAF FDC based on the E/C/F/TAF Phase 2 and Phase 3 studies, the RPV Phase 2 and Phase 3 studies, the Complera/Eviplera Phase 2b and 3 studies, and the FTC/RPV/TAF Phase 1 studies are presented. All laboratory abnormalities discussed in the following sections were treatment emergent and are referred to as laboratory abnormalities in this document.

## 3.1. E/C/F/TAF Studies

Table 79 presents an overall summary of Grade 3 and 4 laboratory abnormalities for the E/C/F/TAF Phase 2 and Phase 3 studies. Approximately 20% of subjects across all E/C/F/TAF studies had a Grade 3 or 4 laboratory abnormality, with the exception of adolescent subjects in Study GS-US-292-0106 (4 subjects, 8.3%). Among the most common Grade 3 or 4 laboratory abnormalities across the E/C/F/TAF studies were creatine kinase, and fasting LDL. In ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111, Grade 3 or 4 creatine kinase abnormalities (E/C/F/TAF 6.8%, 59 subjects; STB 5.7%, 49 subjects) occurred at a variety of time points and were not consistently present for individual subjects, and no case of clinical rhabdomyolysis was reported. Grade 3 or 4 creatine kinase laboratory abnormalities were reported for a similar percentage of subjects in both treatment groups for virologically suppressed subjects (E/C/F/TAF 5.2%, 50 of 959 subjects; FTC/TDF+3rd Agent 5.0%, 24 of 477 subjects). In subjects with mild to moderate renal impairment, Grade 3 or 4 creatine kinase abnormalities were reported for 10 subjects (4.1%) in Cohort 1 (switch) and 1 subject (16.7%) in Cohort 2 (ART-naive). No Grade 3 or 4 creatine kinase abnormalities were reported for ART-naive adolescent subjects.

In E/C/F/TAF ART-naive subjects, Grade 3 LDL abnormalities were reported for 5.0% of subjects (n = 42) in the E/C/F/TAF group and 2.2% of subjects (n = 18) in the STB group. No Grade 4 fasting LDL laboratory abnormalities were reported in either treatment group. In virologically suppressed subjects, more subjects in the E/C/F/TAF group than in the comparator groups had Grade 3 fasting LDL abnormalities (E/C/F/TAF 7.2%, 67 subjects; FTC/TDF+3rd Agent 0.9%, 4 subjects). In subjects with mild to moderate renal impairment, Grade 3 fasting LDL abnormalities were reported for 14 subjects (6.0%), which is consistent with the incidence reported for ART-naive subjects and virologically suppressed subjects. No Grade 3 or 4 fasting LDL abnormalities were reported for ART-naive adolescent subjects.

Lipase testing was only performed in subjects with serum amylase > 1.5 × upper limit of normal. In ART-naive subjects and virologically suppressed subjects in the E/C/F/TAF studies, Grade 3 or 4 lipase abnormalities were reported less frequently in the E/C/F/TAF groups than in the comparator groups.

Among virologically suppressed subjects in Study GS-US-292-0109, a lower percentage of subjects in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group had Grade 3 or 4 abnormalities (E/C/F/TAF 19.8%, FTC/TDF+3rd Agent 25.4%), predominantly driven by the higher incidence of Grade 3 or Grade 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group

(E/C/F/TAF 0.1%, 1 of 959 subjects; FTC/TDF+3rd Agent 14.3%, 68 of 477 subjects). Almost all cases (66 of 68) of Grade 3 or 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group occurred in subjects taking ATV.

The incidence of all other Grade 3 or 4 laboratory abnormalities were generally similar across the 2 treatment groups in each study with a comparator group.

Among subjects with mild to moderate renal impairment, Grade 3 or 4 hypercholesterolemia, serum glucose (nonfasting, hyperglycemia), and urine glucose (glycosuria) were reported in a higher percentage of subjects than in other studies.

**Table 79. E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Grade 3 and 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group from Any Study (Safety Analysis Set)**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects Who Switched Treatment | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Maximum Postbaseline Toxicity Grade | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 172 (20.0%) | 171 (19.8%) | 31 (27.9%) | 11 (19.0%) | 190 (19.8%) | 121 (25.4%) | 64 (26.4%) | 1 (16.7%) | 4 (8.3%) |
| Hematology | | | | | | | | | |
| Neutrophils | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 13 (1.5%) | 21 (2.4%) | 7 (6.3%) | 2 (3.4%) | 11 (1.1%) | 3 (0.6%) | 2 (0. 8%) | 0 | 3 (6.3%) |
| Chemistry | | | | | | | | | |
| ALT | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 10 (1.2%) | 12 (1.4%) | 1 (0.9%) | 1 (1.7%) | 5 (0.5%) | 3 (0.6%) | 2 (0.8%) | 0 | 0 |
| Amylase | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | – |
| Grade 3 or 4 | 13 (1.5%) | 26 (3.0%) | 3 (2.7%) | 2 (3.4%) | 11 (1.1%) | 9 (1.9%) | 6 (2.5%) | 1 (16.7%) | – |
| AST | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 13 (1.5%) | 16 (1.8%) | 1 (0.9%) | 0 | 12 (1.3%) | 5 (1.0%) | 1 (0.4%) | 0 | 0 |
| Creatine Kinase | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 59 (6.8%) | 49 (5.7%) | 7 (6.3%) | 2 (3.4%) | 50 (5.2%) | 24 (5.0%) | 10 (4.1%) | 1 (16.7%) | 0 |
| Creatinine | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 0 | 2 (0.2%) | 0 | 0 | 0 | 0 | 5 (2.1%) | 0 | 0 |
| GGT | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | – |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects Who Switched Treatment | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Grade 3 or 4 | 3 (0.3%) | 12 (1.4%) | 1 (0.9%) | 1 (1.7%) | 4 (0.4%) | 5 (1.0%) | 3 (1.2%) | 0 | – |
| Lipase[b] | 90 | 113 | 8 | 10 | 46 | 30 | 33 | 2 | – |
| Grade 3 or 4 | 4 (4.4%) | 9 (8.0%) | 0 | 1 (10.0%) | 4 (8.7%) | 3 (10.0%) | 4 (12.1%) | 0 | – |
| Serum Glucose (Fasting, Hyperglycemia) | 860 | 865 | 111 | 58 | 958 | 475 | 242 | 6 | 31 |
| Grade 3 or 4 | 7 (0.8%) | 4 (0.5%) | 2 (1.8%) | 1 (1.7%) | 7 (0.7%) | 2 (0.4%) | 6 (2.5%) | 0 | 0 |
| Serum Glucose (Nonfasting, Hyperglycemia)[c] | 858 | 857 | – | – | 959 | 475 | 241 | 6 | 48 |
| Grade 3 or 4 | 7 (0.8%) | 10 (1.2%) | – | – | 5 (0.5%) | 6 (1.3%) | 10 (4.1%) | 0 | 0 |
| Total Bilirubin (Hyperbilirubinemia) | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 0 | 4 (0.5%) | 0 | 0 | 1 (0.1%) | 68 (14.3%) | 0 | 0 | 0 |
| Total Cholesterol (Fasting, Hypercholesterolemia) | 835 | 834 | 110 | 58 | 930 | 454 | 232 | 6 | 23 |
| Grade 3 or 4 | 15 (1.8%) | 10 (1.2%) | 3 (2.7%) | 0 | 28 (3.0%) | 0 | 10 (4.3%) | 0 | 0 |
| Triglycerides (Fasting) | 835 | 834 | 110 | 58 | 930 | 454 | 232 | 6 | 23 |
| Grade 3 or 4 | 4 (0.5%) | 2 (0.2%) | 1 (0.9%) | 1 (1.7%) | 8 (0.9%) | 2 (0.4%) | 1 (0.4%) | 0 | 0 |
| LDL (Fasting) | 835 | 833 | 110 | 58 | 930 | 454 | 232 | 6 | 23 |
| Grade 3 or 4 | 42 (5.0%) | 18 (2.2%) | 10 (9.1%) | 3 (5.2%) | 67 (7.2%) | 4 (0.9%) | 14 (6.0%) | 0 | 0 |

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects Who Switched Treatment | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| | E/C/F/TAF (N=866) | STB (N=867) | E/C/F/TAF (N=112) | STB (N=58) | E/C/F/TAF (N=959) | FTC/TDF+ 3rd Agent (N=477) | ART Experienced E/C/F/TAF (N=242) | ART-Naive E/C/F/TAF (N=6) | E/C/F/TAF (N=48) |
| Uric Acid (Hyperuricemia) | 862 | 865 | 111 | 58 | 959 | 477 | 242 | 6 | 48 |
| Grade 3 or 4 | 0 | 2 (0.2%) | 0 | 0 | 2 (0.2%) | 0 | 4 (1.7%) | 0 | 0 |
| Urinalysis[d] | | | | | | | | | |
| Urine Glucose (Glycosuria) | 862 | 865 | 111 | 58 | 959 | 476 | 242 | 6 | 48 |
| Grade 3 or 4 | 11 (1.3%) | 13 (1.5%) | 2 (1.8%) | 0 | 11 (1.1%) | 5 (1.1%) | 8 (3.3%) | 0 | 0 |
| Urine red blood cell (Hematuria, Quantitative) | 862 | 865 | 111 | 58 | 959 | 476 | 242 | 6 | 48 |
| Grade 3 or 4 | 15 (1.7%) | 19 (2.2%) | 2 (1.8%) | 0 | 18 (1.9%) | 3 (0.6%) | 4 (1.7%) | 0 | 1 (2.1%) |

Denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value (for the test).
Subjects were counted once for the maximum postbaseline severity for each laboratory test.

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. Laboratory abnormalities during the open-label extension were similar to the laboratory abnormalities observed in the randomized phase.

b Lipase test was only performed for subjects with serum amylase > 1.5 x upper limit of normal.

c Nonfasting glucose was not collected at baseline, therefore, treatment emergent cannot be determined. Maximum postbaseline grade was summarized.

d For Urinalysis (ie, urine glucose and urine red blood cell), the highest grade is up to Grade 3.

Source: E/C/F/TAF ISS, Table 19; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 32.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 33; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 45; GS-US-292-0106 Interim CSR, Section 15.1, Table 27

## 3.2. RPV Studies

### 3.2.1. Studies C209 and C215 (FTC/TDF Subset)

Grade 3 and 4 laboratory abnormalities are summarized for the FTC/TDF subset in Table 80.

**Table 80. RPV Studies C209 and C215 (FTC/TDF Subset): Treatment-Emergent Grade 3-4 Laboratory Abnormalities in the RPV or Control Group (Phase 3 Week 96 Pooled Analysis)**

| Laboratory Parameter Abnormality Worst toxicity grade, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 |
| **Grade 3** | **34 (9.9)** | **64 (18.8)** | **23 (11.3)** | **29 (14.8)** | **57 (10.4)** | **93 (17.4)** |
| **Grade 4** | **10 (2.9)** | **13 (3.8)** | **4 (2.0)** | **7 (3.6)** | **14 (2.6)** | **20 (3.7)** |
| **Grade 3 or Grade 4** | **40 (11.6)** | **70 (20.6)** | **27 (13.2)** | **31 (15.8)** | **67 (12.2)** | **101 (18.8)** |
| **General Biochemistry** | | | | | | |
| **Hypocalcemia, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 4 | 1 (0.3) | 0 | 0 | 0 | 1 (0.2) | 0 |
| **Hypophosphatemia, N'** | **345** | **339** | **204** | **196** | **549** | **535** |
| Grade 3 | 6 (1.7) | 6 (1.8) | 1 (0.5) | 4 (2.0) | 7 (1.3) | 10 (1.9) |
| **Hyperkalemia, N'** | **345** | **339** | **204** | **196** | **549** | **535** |
| Grade 4 | 2 (0.6) | 3 (0.9) | 0 | 0 | 2 (0.4) | 3 (0.6) |
| **Hyponatremia, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 0 | 1 (0.3) | 1 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| Grade 4 | 1 (0.3) | 0 | 0 | 0 | 1 (0.2) | 0 |
| **Hypernatremia, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 0 | 0 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Grade 4 | 1 (0.3) | 0 | 0 | 0 | 1 (0.2) | 0 |
| **Hyperuricemia, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 1 (0.3) | 0 | 0 | 0 | 1 (0.2) | 0 |
| **Increased alkaline phosphatase, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 0 | 1 (0.3) | 0 | 0 | 0 | 1 (0.2) |
| **General Hematology** | | | | | | |
| **Decreased Hemoglobin, N'** | **345** | **340** | **204** | **196** | **195** | **549** |
| Grade 3 | 1 (0.3) | 2 (0.6) | 0 | 0 | 0 | 1 (0.2) |
| Grade 4 | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| **Decreased Platelet Count, N'** | **344** | **338** | **204** | **196** | **195** | **548** |
| Grade 3 | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| **Decreased white blood cell Count, N'** | **345** | **340** | **204** | **196** | **195** | **549** |
| Grade 3 | 0 | 1 (0.3) | 1 (0.5) | 0 | 0 | 1 (0.2) |

| Laboratory Parameter Abnormality Worst toxicity grade, n (%) | C209 | | C215 | | Pooled | |
|---|---|---|---|---|---|---|
| | RPV N = 346 | Control N = 344 | RPV N = 204 | Control N = 202 | RPV N = 550 | Control N = 546 |
| **Hepatic Parameters** | | | | | | |
| **Increased AST, N'** | **345** | **339** | **204** | **196** | **549** | **535** |
| Grade 3 | 7 (2.0) | 11 (3.2) | 4 (2.0) | 3 (1.5) | 11 (2.0) | 14 (2.6) |
| Grade 4 | 1 (0.3) | 3 (0.9) | 2 (1.0) | 2 (1.0) | 3 (0.5) | 5 (0.9) |
| **Increased ALT, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 1 (0.3) | 9 (2.6) | 3 (1.5) | 3 (1.5) | 4 (0.7) | 12 (2.2) |
| Grade 4 | 3 (0.9) | 5 (1.5) | 2 (1.0) | 2 (1.0) | 5 (0.9) | 7 (1.3) |
| **Hyperbilirubinemia, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 0 | 2 (0.6) | 3 (1.5) | 0 | 3 (0.5) | 2 (0.4) |
| **Lipids and Glucose (Fasted)** | | | | | | |
| **Increased TC, N'** | **345** | **339** | **204** | **196** | **549** | **535** |
| Grade 3 | 1 (0.3) | 7 (2.1) | 0 | 5 (2.6) | 1 (0.2) | 12 (2.2) |
| **Hyperglycemia, N'** | **345** | **338** | **204** | **196** | **549** | **534** |
| Grade 3 | 1 (0.3) | 1 (0.3) | 1 (0.5) | 0 | 2 (0.4) | 1 (0.2) |
| **Increased LDL, N'** | **345** | **339** | **204** | **195** | **549** | **534** |
| Grade 3 | 4 (1.2) | 13 (3.8) | 1 (0.5) | 8 (4.1) | 5 (0.9) | 21 (3.9) |
| **Increased Triglycerides, N'** | **345** | **339** | **204** | **196** | **549** | **535** |
| Grade 3 | 2 (0.6) | 6 (1.8) | 1 (0.5) | 4 (2.0) | 3 (0.5) | 10 (1.9) |
| Grade 4 | 0 | 3 (0.9) | 0 | 1 (0.5) | 0 | 4 (0.7) |
| **Pancreatic Parameters** | | | | | | |
| **Increased Pancreatic Amylase, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 14 (4.1) | 19 (5.6) | 7 (3.4) | 6 (3.1) | 21 (3.8) | 25 (4.7) |
| Grade 4 | 0 | 0 | 2 (1.0) | 1 (0.5) | 2 (0.4) | 1 (0.2) |
| **Increased Lipase, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 1 (0.3) | 3 (0.9) | 1 (0.5) | 2 (1.0) | 2 (0.4) | 5 (0.9) |
| Grade 4 | 2 (0.6) | 1 (0.3) | 1 (0.5) | 2 (1.0) | 3 (0.5) | 3 (0.6) |
| **Renal Parameters** | | | | | | |
| **Increased Creatinine, N'** | **345** | **340** | **204** | **196** | **549** | **536** |
| Grade 3 | 0 | 0 | 1 (0.5) | 0 | 1 (0.2) | 0 |
| Grade 4 | 0 | 0 | 0 | 1 (0.5) | 0 | 1 (0.2) |

Source: TMC278-C209-W96-Anal-Saf-Lab/Display SAF.23, TMC278-C215-W96-Anal-Saf-Lab/Display SAF.25 and TMC278-C904-W96-Anal-Saf-Lab/Display SAF.35.

For the FTC/TDF subset, the incidence of Grade 3 or 4 laboratory abnormalities was lower in the RPV group (12.2%) than in the control group (18.8%).

For the FTC/TDF subset, the most common Grade 3 and 4 laboratory abnormalities in the RPV group were increased pancreatic amylase (4.2% in the RPV group and 4.9% in the control group), increased AST (2.5% vs 3.5%, respectively), and increased ALT (1.6% vs 3.5%,

respectively). For the FTC/TDF subset, the most common Grade 3 and 4 laboratory abnormalities in the control group were increased LDL cholesterol (3.9% in the control group vs 0.9% in the RPV group), increased pancreatic amylase (4.9% vs 4.2%, respectively), and increased ALT (3.5% vs 1.6%, respectively). No Grade 4 laboratory abnormalities were reported in more than 5 subjects (0.9%) in the RPV group and in more than 7 subjects (1.3%) in the control group.

#### 3.2.1.1. Adverse Events Related to Laboratory Abnormalities

Most laboratory abnormality-related AEs were reported at low incidence. Those laboratory abnormality-related AEs occurring in ≥ 2% of subjects in either the RPV or control group were increased AST (2.5% vs 3.2%, respectively), increased ALT (2.0% vs 3.7%, respectively), anemia (2.0% vs 2.3%, respectively), neutropenia (2.5% vs 1.9%, respectively), decreased blood cortisol (2.9% vs 1.6%, respectively), decreased neutrophil count (1.7% vs 2.3%, respectively), hypercholesterolemia (1.0% [7 subjects] vs 2.5%, respectively), proteinuria (2.0% vs 1.2% [8 subjects], respectively), and hyperlipidemia and hypertriglyceridemia (both 0.4% [3 subjects] vs 2.1%, respectively).

Generally, the incidences of laboratory abnormality-related AEs were similar between the 2 treatment groups, except for metabolism AEs which were observed in a smaller proportion of subjects in the RPV group (5.0%) compared with the control group (10.1%).

Laboratory abnormality-related SAEs, discontinuation for laboratory abnormality-related AEs, and Grade 3 and 4 laboratory abnormalities were rare.

### 3.2.2. Study C213

Most of the worst graded laboratory abnormalities were grade 1-2. The most frequent grade 3-4 laboratory abnormalities were observed for neutrophils and precursors decreased, and neutrophils segmented decreased, which were observed in 3 subjects (1 subject with grade 4 abnormalities for both parameters and 2 subjects with grade 3 abnormalities for both parameters). Grade 4 creatinine increased was reported for 1 subject. Grade 3 amylase increased was reported in 2 subjects (one of which was the subject with the grade 4 creatinine increased) and grade 3 hypophosphatemia was reported in 1 subject (TMC278-C213-W48-CSR, Section 8.3.3).

## 3.3. Complera/Eviplera Studies

### 3.3.1. Study GS-US-264-0111

The majority of treatment-emergent laboratory abnormalities were reported as Grade 1 or Grade 2 as the highest toxicity grade for a given parameter during Study GS-US-264-0111. Grade 3 laboratory abnormalities were reported in 3 of 49 subjects (6.1%) and a Grade 4 laboratory abnormality was reported in 1 subject (2.0%). Two subjects each had a Grade 3 increased creatine kinase value, and a Grade 4 increased creatine kinase value was reported in 1 subject. One of the subjects with Grade 3 increased creatine kinase also had Grade 3 increased serum amylase during the study. Lastly, 1 subject had Grade 3 increased serum amylase during the

study. Both subjects with increased serum amylase had elevated values at screening and baseline. Only the Grade 3 and 4 creatine kinase elevations were considered marked laboratory abnormalities (defined as laboratory values that increased at least 3 toxicity grades from baseline at any postbaseline time point up to 30 days after the last dose). No other Grade 3 or 4 laboratory abnormalities were reported for any other parameter during the study (GS-US-264-0111, Section 11.6).

### 3.3.2. Study GS-US-264-0106

The majority of treatment-emergent laboratory abnormalities were reported as Grade 1 or Grade 2 as the highest toxicity grade for a given parameter. Grade 3 or 4 treatment-emergent laboratory abnormalities are summarized in Table 81.

Individual Grade 3 or 4 treatment-emergent laboratory abnormalities were reported in ≤ 6% of subjects in any treatment group during the study, except for lipase which was only examined in a small subset of subjects in response to elevated amylase levels (Table 81). Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 2 subjects in the FTC/RPV/TDF group included increased creatine kinase (8 subjects), elevated ALT (5 subjects), elevated AST (5 subjects), decreased absolute neutrophil count (3 subjects), increased amylase (3 subjects), increased lipase (3 subjects), and hematuria (5 subjects). Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 2 subjects in the SBR group included increased bilirubin (10 subjects), increased creatine kinase (3 subjects), and elevated AST (3 subjects). After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24, Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 2 subjects in the Delayed Switch group (Weeks 24–48) included increased creatine kinase (7 subjects), elevated ALT (7 subjects), and elevated AST (3 subjects).

Although the Grade 3 or 4 laboratory abnormalities described above were reported most frequently during the study, no clinically meaningful mean changes from baseline were observed overall in these laboratory parameters in any treatment group during the study. Overall, individual AEs of laboratory abnormalities that were considered by the investigator to be related to study drug were reported infrequently (< 2% of subjects in any treatment group). Study drug-related AEs of laboratory abnormalities that were reported in at least 2 subjects in any treatment group included the following: ALT increased (3 subjects [0.9%] in the FTC/RPV/TDF group and 2 subjects [1.3%] in the Delayed Switch group), liver function test abnormal (4 subjects [1.3%] in the FTC/RPV/TDF group and 1 subject [0.7%] in the Delayed Switch group), proteinuria (4 subjects [1.3%] in the FTC/RPV/TDF group and 1 subject [0.7%] in the Delayed Switch group), AST increased (1 subject [0.3%] in the FTC/RPV/TDF group and 1 subject [0.7%] in the Delayed Switch group), and transaminases increased (2 subjects [1.3%] in the Delayed Switch group).

One subject ([redacted] [Delayed Switch group]), 46-year-old male, experienced an SAE of blood creatine phosphokinase increased (Grade 4) during the study (onset, Day 197 and resolution, Day 204). The subject had creatine kinase values ranging from 87 to 128 U/L from baseline through Day 169 (SBR period). On Days 197 and 199, creatine kinase values were 6016 U/L (Grade 4) and 3173 U/L (Grade 3), respectively. Creatine kinase values were normal or high-normal (range: 99 to 543 U/L) on Days 204 through 332. This event was considered by

the investigator to be unrelated to study drug and study drug was continued without interruption. No other SAEs of individual laboratory abnormalities were reported during the study.

**Table 81. Complera/Eviplera Study GS-US-264-0106: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities (Safety Analysis Set)**

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| Subjects With a Maximum Postdose Toxicity Grade 3 or 4 Treatment-Emergent Laboratory Abnormality, n (%) | | | | |
| Grade 3 | 21 (6.6) | 13 (8.2) | 20 (13.2) | 41 (8.7) |
| Grade 4 | 7 (2.2) | 5 (3.1) | 3 (2.0) | 10 (2.1) |
| Absolute Neutrophil Count | | | | |
| Grade 3 | 3 (0.9) | 1 (0.6) | 2 (1.3) | 5 (1.1) |
| ALT | | | | |
| Grade 3 | 4 (1.3) | 1 (0.6) | 6 (3.9) | 10 (2.1) |
| Grade 4 | 1 (0.3) | 0 | 1 (0.7) | 2 (0.4) |
| Amylase (Total Amylase) | | | | |
| Grade 3 | 2 (0.6) | 1 (0.6) | 1 (0.7) | 3 (0.6) |
| Grade 4 | 1 (0.3) | 0 | 0 | 1 (0.2) |
| AST | | | | |
| Grade 3 | 4 (1.3) | 1 (0.6) | 2 (1.3) | 6 (1.3) |
| Grade 4 | 1 (0.3) | 2 (1.3) | 1 (0.7) | 2 (0.4) |
| Bilirubin (Hyperbilirubinemia) | | | | |
| Grade 3 | 0 | 9 (5.7) | 1 (0.7) | 1 (0.2) |
| Grade 4 | 0 | 1 (0.6) | 0 | 0 |
| Cholesterol (Hypercholesterolemia) | | | | |
| Grade 3 | 0 | 1 (0.7) | 0 | 0 |
| Creatine Kinase | | | | |
| Grade 3 | 3 (0.9) | 1 (0.6) | 5 (3.3) | 8 (1.7) |
| Grade 4 | 5 (1.6) | 2 (1.3) | 2 (1.3) | 7 (1.5) |
| Gamma Glutamyl Transferase | | | | |
| Grade 3 | 1 (0.3) | 0 | 1 (0.7) | 2 (0.4) |
| Glucose (Hyperglycemia) | | | | |
| Grade 3 | 1 (0.3) | 1 (0.6) | 1 (0.7) | 2 (0.4) |
| Lipase | | | | |
| Grade 3 | 3 (18.8) | 0 | 0 | 3 (16.7) |
| Triglycerides | | | | |
| Grade 3 | 1 (0.3) | 0 | 0 | 1 (0.2) |
| Grade 4 | 0 | 2 (1.3) | 0 | 0 |
| Urine Glucose (Glycosuria) | | | | |
| Grade 3 | 1 (0.3) | 1 (0.6) | 2 (1.3) | 3 (0.6) |
| Urine Occult Blood (Hematuria) | | | | |
| Grade 3 | 5 (1.6) | 1 (0.6) | 1 (0.7) | 6 (1.3) |
| Urine Protein (Proteinuria) | | | | |
| Grade 3 | 0 | 0 | 1 (0.7) | 1 (0.2) |

Note: Safety Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug. Treatment-emergent laboratory abnormalities were defined as lab values that increase at least 1 toxicity grade from baseline at any postbaseline time point up to 30 days after last dosing date. If baseline data was missing, then any graded abnormality was included. Only cholesterol and triglycerides measured under fasting status were graded for toxicity.

[a] Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

Source: GS-US-264-0106 Week 48 CSR, Section 15.1, Table 5.5.1

## 3.4. FTC/RPV/TAF Studies

### Study GS-US-366-1159

The maximum postdose toxicity for the majority of laboratory abnormalities was Grade 1. Grade 3 abnormalities were reported in 8 subjects (8.3%). All but 1 of the Grade 3 abnormalities were occult blood on urinalysis in female subjects (5 of 8 subjects had confirmed menses). One subject with Grade 1 amylase as screening and baseline had treatment-emergent Grade 2 and 3 amylase as well as Grade 3 and 4 lipase throughout the study without clinical symptoms. At this subject's last assessment on Day 35, amylase was Grade 2, and lipase was Grade 3. There were no other Grade 4 laboratory abnormalities (GS-US-366-1159, Section 11.6).

### Study GS-US-366-1651

For the majority of subjects who had laboratory abnormalities, the maximum postdose toxicity was Grade 1. A Grade 3 laboratory abnormality was reported in 3.3% (2 subjects) and 3.3% (1 subject) following the administration of Treatment A (FTC/RPV/TAF fasted) and Treatment B (FTC/RPV/TAF, fed, moderate-fat), respectively (and 0 subjects following Treatment C, fed, high-calorie, high-fat conditions). All Grade 3 abnormalities were cases of urine occult blood in female subjects due to menses. No subjects had Grade 4 laboratory abnormalities (GS-US-366-1651, Section 11.6).

### Study GS-US-366-1689

The majority of laboratory abnormalities were Grade 1 or 2 in severity. Three subjects had Grade 3 or 4 laboratory abnormalities. Grade 3 laboratory abnormalities included increased LDL (following LDV/SOF, FTC/RPV/TAF, and LDV/SOF+FTC/RPV/TAF), positive occult blood in urine (following FTC/RPV/TAF), and increased AST (following FTC/RPV/TAF). One Grade 4 laboratory abnormality of increased creatine kinase (following FTC/RPV/TAF) was reported (GS-US-366-1689, Section 11.6).

## 3.5. Laboratory Abnormalities

Detailed clinical laboratory evaluation results are available in the respective CSRs.

## 3.6. Fasting Lipid Parameters

### 3.6.1. E/C/F/TAF Studies

#### 3.6.1.1. ART-Naive Subjects

##### 3.6.1.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct LDL, HDL, and triglycerides at Weeks 24 and 48 (Table 82). The median increase from baseline for those parameters was greater in the E/C/F/TAF group compared with

the STB group at Week 48 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, HDL, direct LDL, and triglycerides). Median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.1 (–0.3, 0.5) in the E/C/F/TAF group and 0.0 (−0.5, 0.4) in the STB group ($p < 0.001$ for the difference between treatment groups). Similar results were seen in an analysis excluding subject receiving lipid modifying agents for total cholesterol, direct LDL, HDL, and triglycerides (Table 83).

Consistent with these results, greater percentages of subjects in the E/C/F/TAF group than the STB group had categorical changes in the following National Cholesterol Education Program (NCEP) ATP III lipid classifications from baseline: fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL): E/C/F/TAF 31.0%, 204 of 659 subjects; STB 17.2%, 111 of 646 subjects; fasting direct LDL (< 130 mg/dL to ≥ 130 mg/dL): E/C/F/TAF 23.3%, 143 of 615 subjects; STB 14.8%, 91 of 613 subjects; and triglycerides (< 200 mg/dL to ≥ 200 mg/dL): E/C/F/TAF 13.5%, 98 of 724 subjects; STB 9.1%, 63 of 695 subjects (E/C/F/TAF ISS, Tables 34.1.2, 34.2.2, and 34.4.2). Based on the number of subjects with available data at Week 48, fewer percentages of subjects in the E/C/F/TAF group than the STB group had categorical changes in fasting HDL (≥ 40 mg/dL to < 40 mg/dL): E/C/F/TAF 4.3%, 23 of 532 subjects; STB 7.9%, 41 of 518 subjects (E/C/F/TAF ISS, Table 34.3.2). These small lipid categorical changes were clinically irrelevant and consistent with data from other studies of ABC, d4T, and other non TDF-based NRTIs in ART-naive patients {11417}.

The majority of these lipid abnormalities were Grade 1 or 2.

Graded fasting hypercholesterolemia was more common in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 42.9%, 358 subjects; STB 25.1%, 209 subjects; E/C/F/TAF ISS, Table 18). The majority of hypercholesterolemia abnormalities were Grade 1 (E/C/F/TAF 216 subjects; STB 138 subjects). Grade 2 hypercholesterolemia was reported for 15.2% of subjects (n = 127) in the E/C/F/TAF group and 7.3% of subjects (n = 61) in the STB group. Grade 3 hypercholesterolemia was infrequent and was reported for similar percentages of subjects in each treatment group (E/C/F/TAF 1.8%, 15 subjects; STB 1.2%, 10 subjects). No subject had Grade 4 hypercholesterolemia.

More subjects in the E/C/F/TAF group compared with the STB group had graded abnormalities in fasting LDL (E/C/F/TAF 37.6%, 314 subjects; STB 23.4%, 195 subjects). The majority of these abnormalities were Grade 1 (E/C/F/TAF 176 subjects; STB 127 subjects). Grade 2 fasting LDL laboratory abnormalities were reported for 11.5% of subjects (n = 96) in the E/C/F/TAF group and 6.0% of subjects (n = 50) in the STB group. Grade 3 LDL abnormalities were reported for 5.0% of subjects (n = 42) in the E/C/F/TAF group and 2.2% of subjects (n = 18) in the STB group. No Grade 4 fasting LDL laboratory abnormalities were reported in either treatment group.

Graded abnormalities in fasting triglycerides were infrequent, and reported for similar percentages of subjects in each treatment group (E/C/F/TAF 1.9%, 16 subjects; STB 1.7%, 14 subjects). There were no Grade 1 fasting triglyceride abnormalities. Grade 2 abnormalities were reported for 1.4% of subjects (n = 12) in each treatment group. Grade 3 and 4 triglyceride abnormalities were as follows: Grade 3: 0.1%, 1 subject in each treatment group; Grade 4 E/C/F/TAF 0.4%, 3 subjects; STB 0.1%, 1 subject.

A similar percentage of subjects in both treatment groups had graded fasting hyperglycemia (E/C/F/TAF 15.5%, 133 subjects; STB 14.0%, 121 subjects). The majority of these abnormalities were Grade 1.

AEs related to lipid laboratory test abnormalities were as follows: hyperlipidemia (E/C/F/TAF 1.2%, 10 subjects; STB 0.5%, 4 subjects); dyslipidemia (E/C/F/TAF 1.2%, 10 subjects; STB 0.3%, 3 subjects); hypertriglyceridemia (E/C/F/TAF 0.6%, 5 subjects; STB 0.2%, 2 subjects); hypercholesterolemia (0.3%, 3 subjects in each group); LDL increased and blood triglycerides increased (each 0.1%, 1 subject in each group), lipids abnormal (E/C/F/TAF 0.1%, 1 subject; STB 0 subjects), Type V hyperlipidemia (E/C/F/TAF 0.1%, 1 subject; STB 0 subjects), and blood cholesterol increased (E/C/F/TAF 0 subjects; STB 0.2%, 2 subjects; E/C/F/TAF ISS, Table 7). None of these lipid laboratory test abnormality AEs were serious, and blood triglycerides increased in 1 subject in the E/C/F/TAF group was the only lipid abnormality AE that led to discontinuation of study drugs (E/C/F/TAF ISS, Tables 14 and 16). The following lipid laboratory test abnormality AEs were considered related to study drugs by the investigator: dyslipidemia (E/C/F/TAF 0.2%, 2 subjects; STB 0 subjects), hyperlipidemia (0.2%, 2 subjects in each group), hypertriglyceridemia (E/C/F/TAF 0.2%, 2 subjects; STB 0.1%, 1 subjects), hypercholesterolemia (0.1%, 1 subject in each group), and blood triglycerides increased (E/C/F/TAF 0.1%, 1 subject; STB 0 subjects) (E/C/F/TAF ISS, Table 11).

In the E/C/F/TAF group, 4.4% of subjects (n = 32) were taking lipid modifying medications at study entry, and 3.6% of subjects (n = 31) initiated treatment during the study (E/C/F/TAF ISS, Tables Req6742.3.1 and Req6742.3.2). In the STB group, 5.0% of subjects (n = 43) were taking lipid modifying medications at study entry, and 2.9% of subjects (n = 25) initiated treatment during the study.

One subject in Study GS-US-292-0104 (Subject [redacted] in the E/C/F/TAF group, a 57-year-old male with chronic tobacco use) had an SAE of acute myocardial infarction on Day 213, as well as a nonserious AE of coronary artery disease (ongoing). Both events were considered unrelated to the study drugs by the investigator. The subject had Grade 1 elevations of total cholesterol and LDL on Day 171.After initiating pravastatin on Day 213, values were within the normal range by Day 333. The SAE of acute myocardial infarction resolved on Day 215 and the subject continued to receive study drugs. One subject in Study GS-US-292-0111 (Subject [redacted] in the E/C/F/TAF group) had SAEs of cerebrovascular accident and transient ischemic attack, a nonserious AE of hypertension, and a concurrent nonserious AE of Grade 1 hypercholesterolemia. The subject had Grade 1 abnormalities in total cholesterol and LDL at baseline, and both laboratory values were normal around the time of the events. None of the events were considered related to study drugs by the investigator. No other subject with an AE indicative of cardiovascular disease had any AE related to lipid laboratory tests.

**Table 82. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Fasting Metabolic Assessments Change from Baseline at Week 24 and Week 48 (Safety Analysis Set)**

| | E/C/F/TAF (N=866) | STB (N=867) | p-value |
|---|---|---|---|
| Fasting Total Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 841 | 848 | 0.14 |
| Mean (SD) | 164 (36.2) | 166 (37.1) | |
| Median | 160 | 163 | |
| Q1, Q3 | 138, 186 | 140, 189 | |
| Change at Week 24 | | | |
| N | 799 | 808 | <.001 |
| Mean (SD) | 27 (29.0) | 11 (28.3) | |
| Median | 26 | 11 | |
| Q1, Q3 | 9, 43 | −7, 28 | |
| Change at Week 48 | | | |
| N | 789 | 781 | <.001 |
| Mean (SD) | 31 (29.5) | 14 (29.9) | |
| Median | 29 | 13 | |
| Q1, Q3 | 13, 48 | −6, 31 | |
| Fasting HDL (mg/dL) | | | |
| Baseline | | | |
| N | 841 | 848 | 0.47 |
| Mean (SD) | 46 (13.1) | 45 (12.6) | |
| Median | 44 | 44 | |
| Q1, Q3 | 37, 53 | 37, 52 | |
| Change at Week 24 | | | |
| N | 799 | 808 | <.001 |
| Mean (SD) | 7 (10.0) | 3 (10.2) | |
| Median | 7 | 4 | |
| Q1, Q3 | 1, 13 | −2, 9 | |

| | E/C/F/TAF (N=866) | STB (N=867) | p-value |
|---|---|---|---|
| Change at Week 48 | | | |
| N | 789 | 781 | <.001 |
| Mean (SD) | 7 (10.9) | 4 (10.4) | |
| Median | 7 | 3 | |
| Q1, Q3 | 1, 13 | −2, 10 | |
| Fasting Direct LDL (mg/dL) | | | |
| Baseline | | | |
| N | 837 | 849 | 0.091 |
| Mean (SD) | 105 (31.2) | 108 (33.5) | |
| Median | 101 | 104 | |
| Q1, Q3 | 81, 125 | 85, 126 | |
| Change at Week 24 | | | |
| N | 795 | 808 | <.001 |
| Mean (SD) | 16 (25.3) | 5 (24.8) | |
| Median | 14 | 4 | |
| Q1, Q3 | 0, 30 | −11, 18 | |
| Change at Week 48 | | | |
| N | 785 | 783 | <.001 |
| Mean (SD) | 15 (24.6) | 4 (25.4) | |
| Median | 13 | 2 | |
| Q1, Q3 | 0, 30 | −12, 17 | |
| Fasting Total Cholesterol to HDL Ratio | | | |
| Baseline | | | |
| N | 841 | 848 | 0.069 |
| Mean (SD) | 3.8 (1.10) | 3.9 (1.22) | |
| Median | 3.6 | 3.6 | |
| Q1, Q3 | 3.0, 4.3 | 3.0, 4.5 | |
| Change at Week 24 | | | |
| N | 799 | 808 | 0.006 |
| Mean (SD) | 0.1 (0.96) | 0.0 (1.11) | |
| Median | 0.1 | 0.0 | |
| Q1, Q3 | −0.3, 0.5 | −0.4, 0.4 | |

| | E/C/F/TAF (N=866) | STB (N=867) | p-value |
|---|---|---|---|
| Change at Week 48 | | | |
| N | 789 | 781 | <.001 |
| Mean (SD) | 0.2 (0.96) | 0.0 (1.03) | |
| Median | 0.1 | 0.0 | |
| Q1, Q3 | −0.3, 0.5 | −0.5, 0.4 | |
| Fasting Triglycerides (mg/dL) | | | |
| Baseline | | | |
| N | 841 | 848 | 0.14 |
| Mean (SD) | 116 (82.4) | 120 (81.7) | |
| Median | 95 | 100 | |
| Q1, Q3 | 70, 137 | 73, 140 | |
| Change at Week 24 | | | |
| N | 799 | 808 | <.001 |
| Mean (SD) | 22 (81.3) | 9 (66.1) | |
| Median | 16 | 8 | |
| Q1, Q3 | −9, 52 | −19, 35 | |
| Change at Week 48 | | | |
| N | 789 | 781 | <.001 |
| Mean (SD) | 30 (103.5) | 10 (80.2) | |
| Median | 18 | 6 | |
| Q1, Q3 | −9, 50 | −21, 36 | |

Only laboratory measurements under fasting status were summarized.
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: E/C/F/TAF ISS, Tables 34.1.1, 34.2.1, 34.3.1, 34.4.1, and 34.5

**Table 83. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Fasting Metabolic Assessments (Excluding Subjects Receiving a Lipid Modifying Agent) Change from Baseline at Week 48 (Safety Analysis Set)**

| Laboratory Parameter (mg/dL) | E/C/F/TAF (N=866) | | STB (N=867) | |
|---|---|---|---|---|
| | Baseline | Week 48 | Baseline | Week 48 |
| | mg/dL | Change[a] | mg/dL | Change[a] |
| Total Cholesterol (fasted) | 162 [N=757] | +30 [N=757] | 166 [N=742] | +13 [N=742] |
| HDL-cholesterol (fasted) | 46 [N=757] | +7 [N=757] | 45 [N=742] | +4 [N=742] |
| LDL-cholesterol (fasted) | 104 [N=753] | +15 [N=753] | 107 [N=744] | +3 [N=744] |
| Triglycerides (fasted) | 113 [N=757] | +29 [N=757] | 119 [N=742] | +10 [N=742] |

A lipid modifying agent was defined as medication with Drug Class = 'LIPID MODIFYING AGENTS' and CMDECOD containing the wording of 'STATIN'

a The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

Source: Table req 7329.1.1, 7329.1.2, 7329.1.3 and 7329.1.4

#### 3.6.1.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, increases from baseline were observed for fasting total cholesterol, fasting direct LDL cholesterol, and fasting HDL cholesterol at Weeks 24 and 48 for each treatment group (Table 84). The median increase from baseline was greater in the E/C/F/TAF group compared with the STB group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for all 3 lipid parameters at Week 24, and for fasting total cholesterol and fasting HDL cholesterol at Week 48.

There were no changes from baseline or statistically significant differences between treatment groups for median fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose for either treatment group.

In the randomized phase, graded fasting hypercholesterolemia was more commonly reported in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 56.4%, 62 subjects; STB 29.3%, 17 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1 (E/C/F/TAF 44 subjects; STB 8 subjects). More subjects in the E/C/F/TAF group compared with the STB group had graded abnormalities in fasting LDL (E/C/F/TAF 50.9%, 56 subjects; STB 36.2%, 21 subjects). The majority of these abnormalities were Grade 1 (E/C/F/TAF 32 subjects; STB 10 subjects). Grade 2 fasting LDL was reported for 12.7% of subjects (n = 14) in the E/C/F/TAF groups and 13.8% of subjects (n = 2) in the STB group. Grade 3 fasting LDL was reported for 9.1% of subjects (n = 10) in the E/C/F/TAF group and 5.2% of subjects (n = 3) in the STB group. No Grade 4 fasting LDL abnormalities were reported in either group.

Two subjects (1.8%) in the E/C/F/TAF group and 1 subject (1.7%) in the STB group had AEs of hyperlipidemia considered related to study drugs by the investigator.

More subjects in the E/C/F/TAF group compared with the STB group received concomitant lipid-modifying agents during the randomized phase (E/C/F/TAF 13.4%, 15 subjects; STB 3.4%, 2 subjects). In the E/C/F/TAF group, 8 of the 15 subjects were continuing treatment from baseline, while 7 initiated treatment during the study. In the STB group, 1 subject was continuing treatment from baseline, and 1 subject initiated treatment during the study.

**Table 84. E/C/F/TAF Study GS-US-292-0102: Summary of Fasting Metabolic Assessments Change from Baseline at Week 24 and Week 48 (Safety Analysis Set)**

| Metabolic Assessment | E/C/F/TAF (N=112) | STB (N=58) | p-value[a] |
|---|---|---|---|
| Fasting Total Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 111 | 58 | 0.32 |
| Median | 152 | 156 | |
| Q1, Q3 | 135, 172 | 137, 188 | |
| Change at Week 24 | | | |
| N | 105 | 58 | <.001 |
| Median | 30 | 13 | |
| Q1, Q3 | 11, 45 | −7, 31 | |
| Change at Week 48 | | | |
| N | 104 | 55 | 0.007 |
| Median | 30 | 17 | |
| Q1, Q3 | 8, 52 | 2, 35 | |
| Fasting Direct LDL Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 111 | 58 | 0.39 |
| Median | 96 | 98 | |
| Q1, Q3 | 79, 114 | 81, 121 | |
| Change at Week 24 | | | |
| N | 105 | 58 | <.001 |
| Median | 16 | 3 | |
| Q1, Q3 | 4, 33 | −10, 20 | |
| Change at Week 48 | | | |
| N | 104 | 55 | 0.11 |
| Median | 17 | 11 | |
| Q1, Q3 | 1, 38 | −4, 24 | |

| Metabolic Assessment | E/C/F/TAF (N=112) | STB (N=58) | p-value[a] |
|---|---|---|---|
| Fasting HDL Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 111 | 58 | 0.66 |
| Median | 42 | 43 | |
| Q1, Q3 | 35, 51 | 36, 53 | |
| Change at Week 24 | | | |
| N | 105 | 58 | 0.010 |
| Median | 6 | 2 | |
| Q1, Q3 | 1, 14 | −2, 7 | |
| Change at Week 48 | | | |
| N | 104 | 55 | 0.023 |
| Median | 7 | 3 | |
| Q1, Q3 | 1, 13 | −1, 8 | |
| Fasting Total Cholesterol to HDL Ratio | | | |
| Baseline | | | |
| N | 111 | 58 | 0.94 |
| Median | 3.7 | 3.7 | |
| Q1, Q3 | 2.9, 4.5 | 3.1, 4.5 | |
| Change at Week 24 | | | |
| N | 105 | 58 | 0.42 |
| Median | 0.1 | 0.1 | |
| Q1, Q3 | −0.3, 0.6 | −0.3, 0.4 | |
| Change at Week 48 | | | |
| N | 104 | 55 | 0.34 |
| Median | 0.2 | 0.1 | |
| Q1, Q3 | −0.2, 0.5 | −0.3, 0.5 | |
| Fasting Triglycerides (mg/dL) | | | |
| Baseline | | | |
| N | 111 | 58 | 0.33 |
| Median | 100 | 85 | |
| Q1, Q3 | 63, 137 | 58, 124 | |

| Metabolic Assessment | E/C/F/TAF (N=112) | STB (N=58) | p-value[a] |
|---|---|---|---|
| Change at Week 24 | | | |
| N | 105 | 58 | 0.45 |
| Median | 24 | 21 | |
| Q1, Q3 | −3, 68 | −9, 54 | |
| Change at Week 48 | | | |
| N | 104 | 55 | 0.65 |
| Median | 15 | 22 | |
| Q1, Q3 | −8, 61 | −2, 44 | |
| Fasting Glucose | | | |
| Baseline | | | |
| N | 111 | 58 | 0.54 |
| Median | 89 | 91 | |
| Q1, Q3 | 85, 96 | 84, 97 | |
| Change at Week 24 | | | |
| N | 105 | 58 | 0.70 |
| Median | 3 | 3 | |
| Q1, Q3 | −3, 10 | −3, 7 | |
| Change at Week 48 | | | |
| N | 104 | 55 | 0.75 |
| Median | 4 | 3 | |
| Q1, Q3 | −2, 9 | −3, 13 | |

Only laboratory measurements under fasting status were summarized
a p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 35.1.1, 35.2.1, 35.3.1, 35.4.1, 35.5.1, and 35.6.1

### 3.6.1.2. Virologically Suppressed Subjects in E/C/F/TAF Studies

#### 3.6.1.2.1. Study GS-US-292-0109

There were increases from baseline in fasting values of total cholesterol, LDL cholesterol, and triglycerides in the E/C/F/TAF group, while these parameters remained unchanged or were changed to a relatively smaller extent in the FTC/TDF+3rd Agent group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups; Table 85).

Consistent with these results, of subjects with available data at Week 48, higher percentages in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had the following categorical shifts from baseline based on NCEP ATP III classifications: total cholesterol (< 200 mg/dL to ≥ 200 mg/dL: E/C/F/TAF 34.0%, 168 of 494 subjects; FTC/TDF+3rd Agent 20.2%, 53 of 262 subjects), LDL cholesterol (< 130 mg/dL to ≥ 130 mg/dL: E/C/F/TAF 23.6%, 114 of 483 subjects; FTC/TDF+3rd Agent 13.6%, 34 of 250 subjects), and triglycerides (< 200 mg/dL to ≥ 200 mg/dL: E/C/F/TAF 13.0%, 81 of 621 subjects; FTC/TDF+3rd Agent 8.2%, 25 of 305 subjects).

Increases from baseline in median fasting values for total cholesterol, LDL cholesterol, and triglycerides at Weeks 24 and 48 were consistently observed in the E/C/F/TAF group, regardless of prior treatment regimen.

There were increases in HDL cholesterol in both treatment groups at Week 48 (median [Q1, Q3] changes from baseline: E/C/F/TAF 2 [−4, 8] mg/dL; FTC/TDF+3rd Agent 1 [−4, 5] mg/dL; p = 0.025 for the difference between groups); the increases were not considered clinically relevant.

There were no clinically relevant changes from baseline in the median fasting values for total cholesterol to HDL ratio, or glucose in either treatment group.

Graded fasting hypercholesterolemia was more commonly reported in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group (E/C/F/TAF 46.7%, 434 of 930 subjects; FTC/TDF+3rd Agent 24.2%, 110 of 454 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1 or Grade 2. Grade 3 hypercholesterolemia was reported only for subjects in the E/C/F/TAF group (3.0%, 28 subjects). Graded abnormalities in fasting LDL cholesterol were also reported for a higher percentage of subjects in the E/C/F/TAF group than the FTC/TDF+3rd Agent group (E/C/F/TAF 37.8%, 352 subjects; FTC/TDF+3rd Agent 16.7%, 76 subjects). The majority of the abnormalities in fasting LDL cholesterol were Grade 1 or Grade 2. Grade 3 fasting LDL abnormalities were reported for 7.2% of subjects (n = 67) in the E/C/F/TAF group and 0.9% of subjects (n = 4) in the FTC/TDF+3rd Agent group. No Grade 4 fasting total cholesterol or fasting LDL abnormalities were reported in either group.

Similar percentages of subjects in each group had hypertriglyceridemia (E/C/F/TAF 2.3%, 21 subjects; FTC/TDF+3rd Agent 0.9%, 4 subjects); Grade 3 or 4 abnormalities of fasting triglycerides were uncommon (E/C/F/TAF 0.9%, 8 subjects; FTC/TDF+3rd Agent 0.4%, 2 subjects; Table 79).

Adverse events related to lipid abnormalities were more commonly reported in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group: hyperlipidemia (E/C/F/TAF 1.9%, 18 subjects; FTC/TDF+3rd Agent 0.8%, 4 subjects); hypercholesterolemia (E/C/F/TAF 2.0%, 19 subjects; FTC/TDF+3rd Agent 0%); dyslipidemia (E/C/F/TAF 0.4%, 4 subjects; FTC/TDF+3rd Agent 0.4%, 2 subjects); hypertriglyceridemia (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); and blood cholesterol increased (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject). All of these AEs were nonserious and none led to discontinuation of study drugs.

The percentage of subjects who received concomitant lipid modifying agents during the study (ie, between the first dose date and the last dose date of study drug, inclusive) was comparable between treatment groups (E/C/F/TAF 14.9%, 143 subjects; FTC/TDF+3rd Agent 13.4%, 64 subjects). Similar percentages of subjects in both treatment groups were taking treatment with lipid modifying agents at study entry (E/C/F/TAF 10.7%, 103 subjects; FTC/TDF+3rd Agent 10.5%, 50 subjects) and initiated treatment with lipid modifying agents during the study (E/C/F/TAF 5.4%, 52 subjects; FTC/TDF+3rd Agent 3.8%, 18 subjects). In this analysis, subjects who stopped treatment that was ongoing at study entry and reinitiated treatment during the study with the same or different lipid modifying agent were counted twice, ie, once as taking a lipid modifying agent at study entry and the second time as initiating a lipid modifying agent during the study.

**Table 85. E/C/F/TAF Study GS-US-292-0109: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set)**

| Metabolic Assessment | E/C/F/TAF (N = 959) | | FTC/TDF+3rd Agent (N = 477) | | P-Value[a] |
|---|---|---|---|---|---|
| | N | Median (Q1, Q3) | N | Median (Q1, Q3) | |
| Fasting Total Cholesterol (mg/dL) | | | | | |
| Baseline | 942 | 182 (156, 208) | 467 | 181 (158, 205) | 0.60 |
| Change at Week 24 | 911 | 21 (4, 40) | 444 | 1 (−13, 16) | < 0.001 |
| Change at Week 48 | 758 | 20 (1, 41) | 367 | 6 (−9, 19) | < 0.001 |
| Fasting Direct LDL Cholesterol (mg/dL) | | | | | |
| Baseline | 942 | 116 (94, 142) | 467 | 116 (96, 139) | 0.97 |
| Change at Week 24 | 911 | 11 (−3, 27) | 444 | −2 (−15, 9) | < 0.001 |
| Change at Week 48 | 757 | 9 (−9, 25) | 367 | 0 (−13, 11) | < 0.001 |
| Fasting HDL Cholesterol (mg/dL) | | | | | |
| Baseline | 942 | 50 (42, 59) | 466 | 49 (42, 58) | 0.48 |
| Change at Week 24 | 911 | 2 (−3, 8) | 443 | 0 (−5, 5) | < 0.001 |
| Change at Week 48 | 758 | 2 (−4, 8) | 366 | 1 (−4, 5) | 0.025 |
| Fasting Total Cholesterol to HDL Ratio | | | | | |
| Baseline | 942 | 3.6 (2.9, 4.5) | 466 | 3.6 (3.0, 4.4) | 0.98 |
| Change at Week 24 | 911 | 0.2 (−0.1, 0.7) | 443 | 0.1 (−0.3, 0.4) | < 0.001 |
| Change at Week 48 | 758 | 0.2 (−0.2, 0.7) | 366 | 0.1 (−0.3, 0.4) | < 0.001 |
| Fasting Triglycerides (mg/dL) | | | | | |
| Baseline | 942 | 120 (82, 169) | 466 | 114 (81, 164) | 0.31 |
| Change at Week 24 | 911 | 10 (−21, 47) | 443 | 2 (−29, 28) | < 0.001 |
| Change at Week 48 | 758 | 10 (−18, 48) | 366 | 0 (−28, 27) | < 0.001 |
| Fasting Glucose (mg/dL) | | | | | |
| Baseline | 940 | 92 (85, 99) | 466 | 92 (86, 100) | 0.40 |
| Change at Week 24 | 908 | 2 (−5, 8) | 447 | 1 (−6, 7) | 0.12 |
| Change at Week 48 | 759 | 2 (−5, 8) | 370 | 0 (−6, 7) | 0.19 |

a P-values comparing the 2 treatment groups were from the 2-sided Wilcoxon rank sum test.
Only laboratory measurements under fasting status were summarized
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 38.1 to 38.6

#### 3.6.1.2.2. Study GS-US-292-0102 Open-Label Extension

In the all TDF to TAF group of Study GS-US-292-0102, increases from baseline at Week 24 were observed for the following (median change from baseline):

- Fasting total cholesterol: 24 mg/dL
- Fasting direct LDL cholesterol: 16 mg/dL
- Fasting HDL cholesterol: 5 mg/dL
- Fasting triglycerides: 10 mg/dL

No changes from baseline were observed in median fasting total cholesterol to HDL ratio.

In the D/C/F/TAF to E/C/F/TAF group, decreases from baseline at Week 24 were observed for the following (median change from baseline):

- Fasting direct LDL cholesterol: −10 mg/dL
- Fasting triglycerides: −12 mg/dL

In the D/C/F/TAF to E/C/F/TAF group, no changes from baseline were observed in fasting total cholesterol or median fasting total cholesterol to HDL ratio.

Serious AEs of acute myocardial infarction and congestive cardiac failure were reported on Day 92 for Subject [redacted] in the D/C/F/TAF to E/C/F/TAF group. This 55-year-old [redacted] female had a pre-existing history of uncontrolled Type 2 diabetes, hypertension, obesity (BMI 33.8 kg/$m^2$), coronary artery disease, and hyperlipidemia. The events resolved on Day 101, were not considered related to the study drugs by the investigator, and did not result in discontinuation of study treatment.

3.6.1.3. Subjects with Mild to Moderate Renal Impairment

3.6.1.3.1. Study GS-US-292-0112

For each baseline eGFR group among Cohort 1 switch subjects and for ART-naive subjects in Cohort 2, changes from baseline to Weeks 24 or 48 were observed for fasting total cholesterol, fasting direct LDL cholesterol, and fasting HDL cholesterol, fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose that demonstrated a trend toward increase in most parameters evaluated (Table 86).

Among Cohort 1 switch subjects, Grade 3 fasting hypercholesterolemia was reported in 4 subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 6 subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group. Grade 3 fasting triglyceridemia was reported in 1 subject in the baseline $eGFR_{CG} < 50$ mL/min group only. Grade 3 fasting LDL was reported in 4 subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 10 subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group. No Grade 4 fasting total cholesterol, triglycerides, or LDL abnormalities were reported in either group. Grade 3 fasting serum glucose (hyperglycemia only) was reported in 4 subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 2 subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group. No Grade 4 fasting serum glucose (both hyperglycemia and hypoglycemia) was reported in either group.

Consistent with these results, based on the number of subjects with available data at Week 48, the following percentages of subjects had categorical changes in the following NCEP ATP III lipid classifications from baseline: fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL): 33.7%, 29 of 86 subjects; fasting direct LDL (< 130 mg/dL to ≥ 130 mg/dL): 21.0%, 21 of 100 subjects; fasting HDL (≥ 40 mg/dL to < 40 mg/dL): 12.7%, 18 of 142 subjects; and triglycerides (< 200 mg/dL to ≥ 200 mg/dL): 13.6%, 17 of 125 subjects.

Two subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group had AEs of hypercholesterolemia and 1 subject in the baseline $eGFR_{CG} \geq 50$ mL/min group had an AE of hyperlipidemia considered related to study drugs by the investigator.

A similar percentage of subjects in the baseline eGFR groups received concomitant lipid-modifying agents (56.3% of subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 46.3% of subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group).

**Table 86. E/C/F/TAF Study GS-US-292-0112: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set)**

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min** | **Total** |
| Fasting Total Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 79 | 160 | 239 |
| Median | 196 | 201 | 198 |
| Q1, Q3 | 173, 240 | 174, 229 | 173, 230 |
| Change at Week 24 | | | |
| N | 73 | 154 | 227 |
| Median | 9 | 12 | 10 |
| Q1, Q3 | −20, 34 | −12, 31 | −15, 32 |
| Change at Week 48 | | | |
| N | 42 | 120 | 162 |
| Median | 11 | 13 | 13 |
| Q1, Q3 | −7. 35 | −15, 35 | −12, 35 |
| Fasting Direct LDL Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 79 | 160 | 239 |
| Median | 122 | 125 | 123 |
| Q1, Q3 | 94, 152 | 99, 151 | 98, 151 |

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min** | **Total** |
| Change at Week 24 | | | |
| N | 73 | 154 | 227 |
| Median | 2 | 7 | 5 |
| Q1, Q3 | −20, 21 | −13, 21 | −16, 21 |
| Change at Week 48 | | | |
| N | 42 | 120 | 162 |
| Median | 2 | 5 | 4 |
| Q1, Q3 | −10, 27 | −11, 29 | −11, 28 |
| Fasting HDL Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 79 | 160 | 239 |
| Median | 55 | 54 | 54 |
| Q1, Q3 | 42, 71 | 46, 65 | 44, 67 |
| Change at Week 24 | | | |
| N | 73 | 154 | 227 |
| Median | −1 | 0 | 0 |
| Q1, Q3 | −8, 4 | −6, 7 | −7, 6 |
| Change at Week 48 | | | |
| N | 42 | 120 | 162 |
| Median | −3 | 1 | −1 |
| Q1, Q3 | −10, 1 | −6, 7 | −7, 6 |
| Fasting Total Cholesterol to HDL Ratio | | | |
| Baseline | | | |
| N | 79 | 160 | 239 |
| Median | 3.7 | 3.6 | 3.6 |
| Q1, Q3 | 2.7, 4.8 | 2.9, 4.6 | 2.9, 4.7 |
| Change at Week 24 | | | |
| N | 73 | 154 | 227 |
| Median | 0.2 | 0.2 | 0.2 |
| Q1, Q3 | −0.3, 0.6 | −0.3, 0.6 | −0.3, 0.6 |
| Change at Week 48 | | | |
| N | 42 | 120 | 162 |

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min** | **Total** |
| Median | 0.5 | 0.1 | 0.3 |
| Q1, Q3 | 0.2, 1.2 | −0.3, 0.7 | −0.2, 0.8 |
| Fasting Triglycerides (mg/dL) | | | |
| Baseline | | | |
| N | 79 | 160 | 239 |
| Median | 143 | 138 | 141 |
| Q1, Q3 | 102, 220 | 92, 198 | 95, 202 |
| Change at Week 24 | | | |
| N | 73 | 154 | 227 |
| Median | 4 | 4 | 4 |
| Q1, Q3 | −39, 42 | −41, 36 | −41, 38 |
| Change at Week 48 | | | |
| N | 42 | 120 | 162 |
| Median | 43 | 6 | 10 |
| Q1, Q3 | 1, 86 | −31, 37 | −18, 45 |
| Fasting Glucose (mg/dL) | | | |
| Baseline | | | |
| N | 78 | 159 | 237 |
| Median | 95 | 94 | 95 |
| Q1, Q3 | 89, 103 | 87, 103 | 87, 103 |
| Change at Week 24 | | | |
| N | 73 | 153 | 226 |
| Median | 3 | −1 | 0 |
| Q1, Q3 | −5, 14 | −9, 5 | −8, 8 |
| Change at Week 48 | | | |
| N | 43 | 121 | 164 |
| Median | 2 | −1 | 0 |
| Q1, Q3 | −11, 8 | −8, 6 | −9, 7 |

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 49.1.1 to 49.1.6

Subjects in Cohort 1 with pre-switch TDF use were compared with subjects who did not receive TDF at baseline, change from baseline at Week 24 for fasting total cholesterol, fasting direct LDL cholesterol, and fasting HDL cholesterol, fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose (Table 87). For the metabolic laboratory parameters evaluated, median changes from baseline at Weeks 24 and 48 demonstrated a trend toward increase in all

parameters for subjects with pre-switch TDF use and a decrease in most parameters for subjects without pre-switch TDF use.

**Table 87. E/C/F/TAF Study GS-US-292-0112: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 With or Without TDF or Without TDF Use at Baseline (Cohort 1 switch Subjects Only, Safety Analysis Set)**

| | With TDF Use at Baseline[a] N=158 | Without TDF Use at Baseline N=84 |
|---|---|---|
| Fasting Total Cholesterol (mg/dL) | | |
| Change at Week 24 | | |
| N | 150 | 77 |
| Median | 20 | −11 |
| Q1, Q3 | −1, 37 | −28, 19 |
| Change at Week 48 | | |
| N | 110 | 52 |
| Median | 21 | −9 |
| Q1, Q3 | 2, 44 | −26, 15 |
| Fasting Direct LDL Cholesterol (mg/dL) | | |
| Change at Week 24 | | |
| N | 150 | 77 |
| Median | 11 | −10 |
| Q1, Q3 | −5, 25 | −30, 12 |
| Change at Week 48 | | |
| N | 110 | 52 |
| Median | 9 | −3 |
| Q1, Q3 | −5, 30 | −26, 5 |
| Fasting HDL Cholesterol (mg/dL) | | |
| Change at Week 24 | | |
| N | 150 | 77 |
| Median | 2 | −4 |
| Q1, Q3 | −4, 7 | −10, 2 |
| Change at Week 48 | | |
| N | 110 | 52 |
| Median | 1 | −3 |
| Q1, Q3 | −5, 7 | −9, 3 |

| | With TDF Use at Baseline[a] N=158 | Without TDF Use at Baseline N=84 |
|---|---|---|
| Fasting Total Cholesterol to HDL Ratio | | |
| Change at Week 24 | | |
| N | 150 | 77 |
| Median | 0.2 | 0.2 |
| Q1, Q3 | −0.2 0.6 | −0.5, 0.6 |
| Change at Week 48 | | |
| N | 110 | 52 |
| Median | 0.4 | 0.2 |
| Q1, Q3 | −0.2, 0.8 | −0.1, 0.7 |
| Fasting Triglycerides (mg/dL) | | |
| Change at Week 24 | | |
| N | 150 | 77 |
| Median | 9 | −10 |
| Q1, Q3 | −33, 42 | −55, 27 |
| Change at Week 48 | | |
| N | 110 | 52 |
| Median | 18 | −1 |
| Q1, Q3 | −13, 48 | −28, 35 |
| Fasting Glucose (mg/dL) | | |
| Change at Week 24 | | |
| N | 150 | 76 |
| Median | 0 | −1 |
| Q1, Q3 | −6, 8 | −10, 8 |
| Change at Week 48 | | |
| N | 113 | 51 |
| Median | 0 | −3 |
| Q1, Q3 | −8, 7 | −11, 6 |

a With TDF use at baseline defined as subjects who took TDF containing regimen (such as Stribild, Atripla, Complera/Eviplera, Truvada, and Viread) immediately prior to the first dose date of study drug.

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 49.2.1 to 49.2.6

Among the 6 ART-naive subjects in Cohort 2, no Grade 3 to 4 fasting total cholesterol, triglycerides, or LDL abnormalities were reported, and no subjects had graded triglyceride values. Based on the number of subjects with available data at Week 48, no Cohort 2 ART-naive subject had a categorical change in NCEP ATP III lipid classifications from baseline for fasting HDL (≥ 40 mg/dL to < 40 mg/dL) or triglycerides (< 200 mg/dL to ≥ 200 mg/dL). Three of 3 subjects and 1 of 2 subjects had a categorical change in NCEP ATP III lipid classifications from baseline for fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL) and fasting direct LDL (<130 mg/dL to ≥ 130 mg/dL), respectively. One subject had an AE of hyperlipidemia considered related to study drug by the investigator and 1 subject received a concomitant lipid-modifying agent (pravastatin).

3.6.1.4. ART-Naive Adolescent Subjects

3.6.1.4.1. Study GS-US-292-0106

Median (Q1, Q3) values at baseline and Week 24, and median changes from baseline at Week 24 in fasting glucose and lipid parameters in Study GS-US-292-0106 are shown in Table 88.

**Table 88. E/C/F/TAF Study GS-US-292-0106: Summary of Fasting Glucose and Lipid Parameters at Week 24 (Safety Analysis Set)**

| Fasting Parameter[a] | Baseline (N = 46) | Week 24 (N = 23) | Change from Baseline at Week 24 (N = 22) |
|---|---|---|---|
| Total Cholesterol (mg/dL) | 130 (116, 148) | 162 (138, 192) | 34 (22, 41) |
| LDL Cholesterol (mg/dL) | 83 (68, 99) | 96 (80, 123) | 18 (5, 30) |
| HDL Cholesterol (mg/dL) | 36 (32, 40) | 51 (41, 57) | 10 (4, 21) |
| Total Cholesterol to HDL Cholesterol Ratio | 3.68 (3.32, 4.17) | 3.49 (2.85, 4.06) | 0.01 (−0.64, 0.34) |
| Triglycerides (mg/dL) | 85 (69, 113) | 95 (77, 112) | 5 (−18, 30) |
| Glucose (mg/dL)[b] | 81 (77, 85) | 84 (81, 89) | 6 (−1, 12) |

a All values are median (Q1, Q3).
b Baseline n = 47
Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 31.1 to 31.6

There were no graded abnormalities in fasting glucose values. Graded abnormalities in fasting total cholesterol and fasting LDL cholesterol were reported for 30.4% of subjects, all of which were Grade 1 or Grade 2 in severity and transient.

For 22 subjects who had nonmissing values at each time point, the following shifts were noted based on NCEP Expert Panel on Cholesterol Levels in Children criteria:

- Total cholesterol: 31.8% of subjects were in a higher category at Week 24 than at baseline
- LDL cholesterol: 31.8% of subjects were in a higher category at Week 24 than at baseline

- HDL cholesterol: 68.2% of subjects were in a higher category at Week 24 than at baseline
- Triglycerides: 36.4% of subjects were in a higher category at Week 24 than at baseline, 13.6% of subjects were in a lower category at Week 24 than at baseline

## 3.6.2. RPV Studies

### 3.6.2.1. ART Naive Subjects

#### 3.6.2.1.1. Studies C209 and C215

Mean change from baseline in TC, LDL, HDL, and triglycerides for the FTC/TDF subset are presented in Table 89.

**Table 89. RPV Studies C209 and C215 (FTC/TDF Subset): Mean Change from Baseline at Week 96 in Lipid Values Reported in Subjects in the RPV or Control Group (Phase 3 Week 96 Pooled Analysis)**

| Laboratory Parameter (mg/dL) | Pooled | | | |
|---|---|---|---|---|
| | RPV N = 550 | | Control N = 546 | |
| Week 96 | Mean (SD) baseline | Mean (SD) change from baseline | Mean (SD) baseline | Mean (SD) change from baseline |
| Total Cholesterol (fasted) | 164.37 (34.772) | 1.39 (27.488) | 188.94 (39.387) | 27.37 (35.794) |
| HDL-Cholesterol (fasted) | 45.33 (12.311) | 3.61 (9.840) | 50.06 (13.135) | 10.81 (10.895) |
| LDL-Cholesterol (fasted) | 96.78 (29.271) | -0.68 (23.901) | 110.81 (33.456) | 14.22 (27.916) |
| Triglycerides (fasted) | 111.51 (72.884) | -13.59 (78.992) | 142.46 (102.869) | 8.21 (103.205) |

Source: TMC278-C904-W96-Anal-Saf-Lab/Display Ad Hoc.

For the FTC/TDF subset, there were no changes from baseline at Week 96 for TC, LDL, and HDL in the RPV group, compared with increases in the control group. Mean decreases from baseline were observed for triglyceride values over the 96-week treatment period in the RPV group, compared with mean increases from baseline in the control group. Similar results were seen in an analysis excluding subject receiving lipid modifying agents (Table 90).

**Table 90. RPV Studies C209 and C215 (FTC/TDF Subset): Mean Change from Baseline at Week 96 in Lipid Values Reported in Subjects Not Receiving a Lipid Modifying Agent in the RPV or Control Group (Phase 3 Week 96 Pooled Analysis)**

| Laboratory Parameter (mg/dL) | Pooled | | | |
|---|---|---|---|---|
| | RPV N = 550 | | Control N = 546 | |
| Week 96 | Baseline | Change from baseline[a] | Baseline | Change from baseline[a] |
| Total Cholesterol (fasted) | 162 [N=430] | 2 [N=430] | 160 [N=401] | 26 [N=401] |
| HDL-Cholesterol (fasted) | 42 [N=429] | 4 [N=429] | 40 [N=399] | 11 [N=399] |
| LDL-Cholesterol (fasted) | 97 [N=427] | -1 [N=427] | 96 [N=397] | 14 [N=397] |
| Triglycerides (fasted) | 123 [N=430] | -14 [N=430] | 127 [N=401] | 6 [N=401] |

a. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values
Source: {34797}

### 3.6.2.2. ART Naive Adolescent Subjects

#### 3.6.2.2.1. Study C213

Mean changes from baseline in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides over time are presented in Figure 25, Figure 26, Figure 27, and Figure 28, respectively.

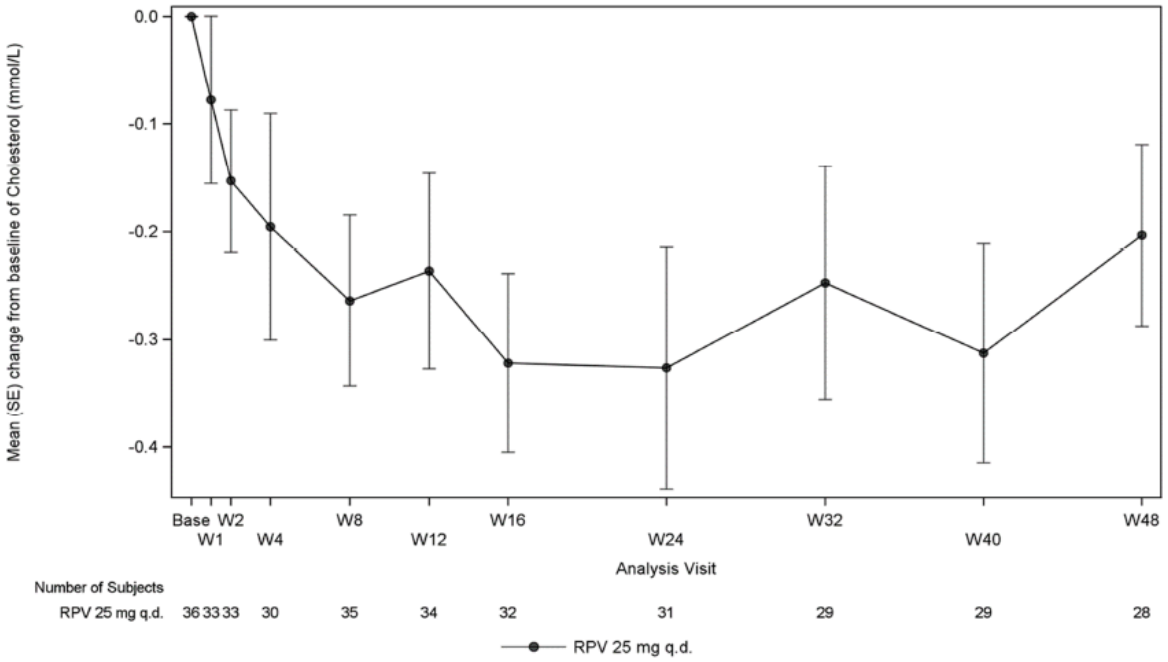
Mean decreases from baseline in total cholesterol were observed up to Week 48 with a mean (SE) decrease from baseline of -0.20 (0.084) mmol/L at Week 48.

Up to Week 4, mean HDL cholesterol remained around baseline. After an initial mean decrease from baseline at Week 8, mean increases from baseline were observed up to Week 48 with a mean (SE) increase from baseline of 0.11 (0.054) mmol/L at Week 48.

Mean decreases from baseline in LDL cholesterol were observed at all time points in the 48-week treatment period. At Week 48, a mean (SE) decrease from baseline of -0.24 (0.080) mmol/L was observed.

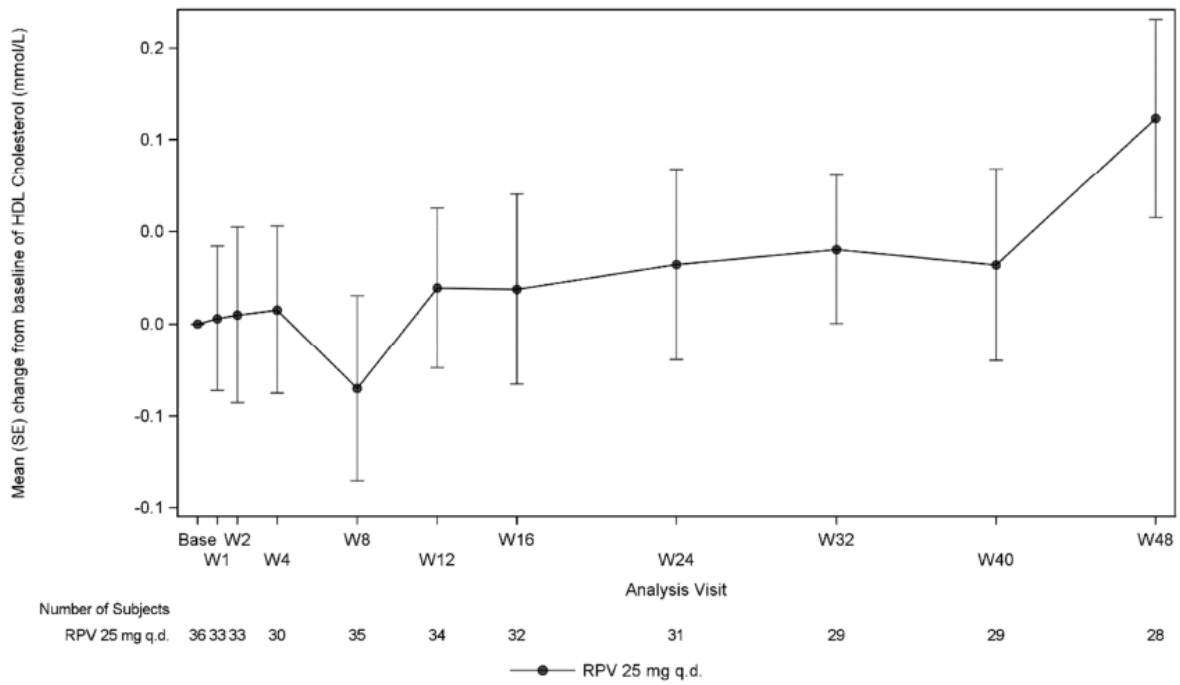
Mean decreases from baseline in triglycerides were observed throughout the 48-week treatment period. At Week 48, a mean (SE) decrease from baseline of -0.16 (0.073) mmol/L was observed.

**Figure 25** **RPV Study C213: Mean (SE) Changes From Baseline in Total Cholesterol (mmol/L) Over Time (Intent-to-Treat)**



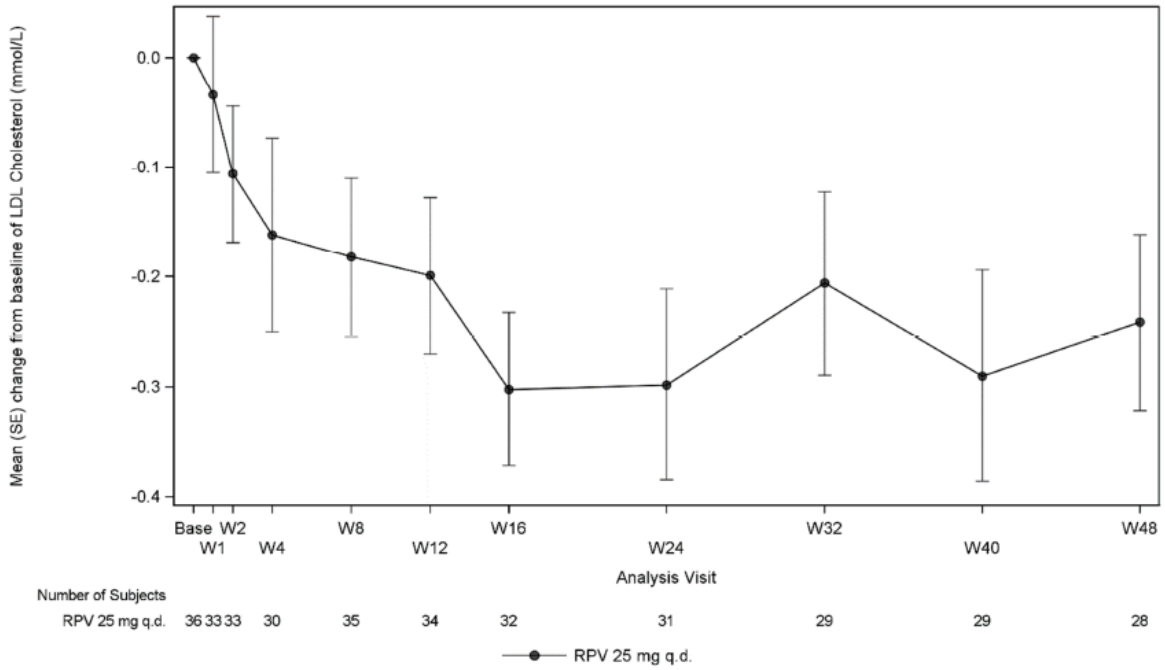

Source: TMC278-C213-W48-CSR/Figure 16

**Figure 26** **RPV Study C213: Mean (SE) Changes From Baseline in HDL Cholesterol (mmol/L) Over Time (Intent-to-Treat)**



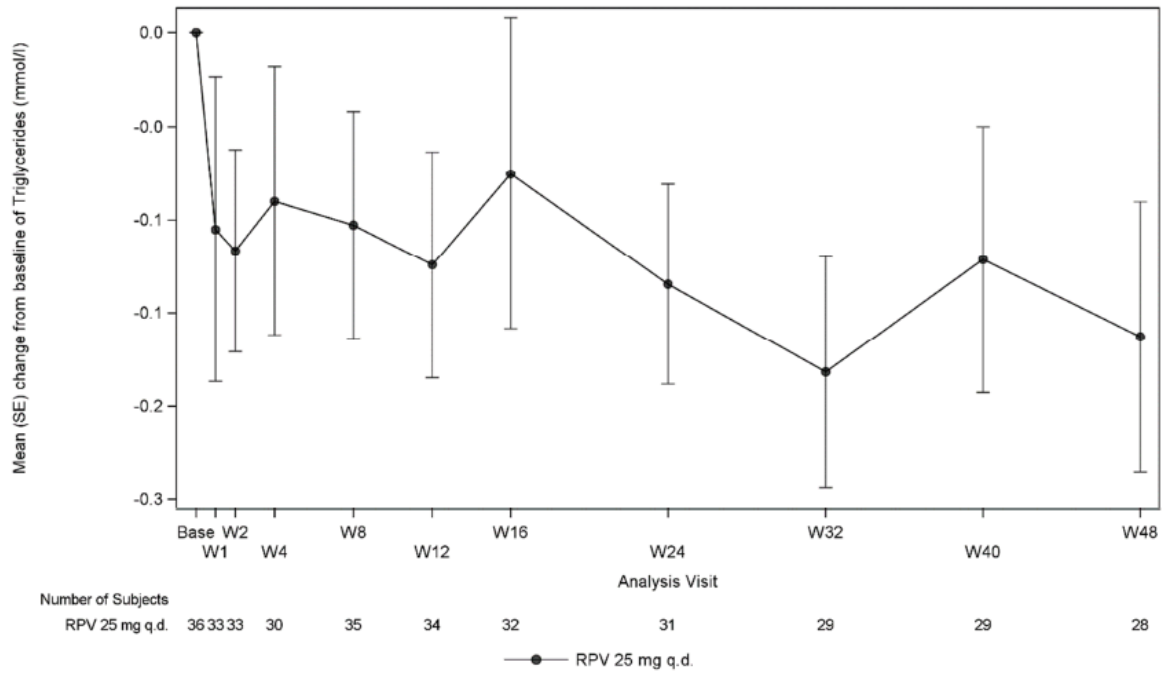

Source: TMC278-C213-W48-CSR/Figure 17

**Figure 27** **RPV Study C213: Mean (SE) Changes From Baseline in LDL Cholesterol (mmol/L) Over Time (Intent-to-Treat)**




Source: TMC278-C213-W48-CSR/Figure 18

**Figure 28** **RPV Study C213: Mean (SE) Changes From Baseline in Triglycerides (mmol/L) Over Time (Intent-to-Treat)**




Source: TMC278-C213-W48-CSR/Figure 19

### 3.6.3. Complera/Eviplera Studies

#### 3.6.3.1. Virologically Suppressed Subjects

##### 3.6.3.1.1. Study GS-US-264-0111

Median values and median change from baseline at Week 48 for fasting lipid parameters are presented in Table 91. Significant decreases from baseline in fasting total cholesterol, direct LDL cholesterol, and fasting triglycerides were observed starting as early as Week 12 and continuing through Week 48. There were statistically significant decreases in fasting total cholesterol, triglycerides, and direct LDL cholesterol from baseline to Week 48 (median change of –17 mg/dL from baseline in total cholesterol and –26 mg/dL in triglycerides [$p < 0.001$ from Wilcoxon signed rank test for both parameters], and –8 in direct LDL cholesterol [$p = 0.016$ from Wilcoxon signed rank test]).

**Table 91. Complera/Eviplera Study GS-US-264-0111: Median (Q1, Q3) of Observed Fasting Lipid Parameters and Changes from Baseline (mg/dL; Safety Analysis Set)**

| Fasting Lipid Parameter | Baseline Median (Q1, Q3) N = 48[a] | Week 48 Median (Q1, Q3) N = 47 | Median of Change from Baseline at Week 48 (Q1, Q3) N = 46[b] | p-value[c] |
|---|---|---|---|---|
| **Total Cholesterol** | 177 (159, 210) | 159 (147, 194) | –17 (–38, 1) | < 0.001 |
| **Direct LDL Cholesterol** | 113 (93, 132) | 103 (82, 121) | –8 (–29, 7) | 0.016 |
| **HDL Cholesterol** | 49 (41, 58) | 45 (40, 53) | –2 (–6, 2) | 0.077 |
| **Triglycerides** | 114 (86, 147) | 92 (72, 136) | –26 (–50, –2) | < 0.001 |
| **Ratio of Total Cholesterol to HDL Cholesterol** | 3.86 (2.97, 4.42) | 3.36 (2.96, 3.98) | –0.17 (–0.58, 0.19) | 0.14 |

a For baseline direct LDL cholesterol, N = 49.

b For the median of change from baseline at Week 48 for direct LDL cholesterol, N = 47.

c P-value for comparison to baseline within treatment group is from Wilcoxon signed rank test.

Source: GS-US-264-0111 CSR, Section 15.1, Tables 5.4.2−5.4.6

##### 3.6.3.1.2. Study GS-US-264-0106

At baseline, the mean (SD) values for lipid parameters were generally similar between the FTC/RPV/TDF and SBR groups (overall analysis). The mean (SD) values for fasting total cholesterol were 192 (41.8) mg/dL in the FTC/RPV/TDF group and 194 (36.5) mg/dL in the SBR group. The mean (SD) values for fasting HDL cholesterol were 53 (15.9) mg/dL in the FTC/RPV/TDF group and 50 (12.0) mg/dL in the SBR group. The mean (SD) values for fasting direct LDL cholesterol were 121 (35.1) mg/dL in the FTC/RPV/TDF group and 124 (31.3) mg/dL in the SBR group. The mean (SD) values for fasting triglycerides were 163 (136.2) mg/dL in the FTC/RPV/TDF group and 173 (107.9) mg/dL in the SBR group. The mean (SD)

values for the ratio of fasting total cholesterol/HDL cholesterol were 3.86 (1.250) in the FTC/RPV/TDF group and 4.08 (1.111) in the SBR group.

Overall, fasting total cholesterol, HDL cholesterol, direct LDL cholesterol, fasting triglycerides, and the ratio of total cholesterol/HDL cholesterol decreased to a greater extent through Week 24 among subjects in the randomized FTC/RPV/TDF group versus those maintaining their baseline PI/r + 2 NRTIs regimen (SBR group) (Table 92). Differences between these treatment groups for all 5 of these lipid parameters were statistically significant at Week 24 ($p < 0.001$). The mean reductions from baseline in lipid parameters observed at Week 24 in the FTC/RPV/TDF group were generally maintained through Week 48 of therapy. After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24, similar decreases in lipid parameters were observed in the Delayed Switch group over Weeks 24 to 48 of the study. Mean values and mean changes from baseline in fasting lipid parameters are also presented in GS-US-264-0106 Week 48 CSR, Section 11.7.6.

Subjects in both treatment arms with prior use of RTV-boosted lopinavir (LPV/r) had higher baseline values for all serum lipid parameters than those without prior LPV/r use. This is consistent with the known elevating effect of LPV/r on total cholesterol and triglycerides {21225} and with recent publications suggesting that lower exposure to LPV/r could be associated with a significant decrease in triglycerides in virologically controlled HIV-1 infected adults {22302}. In general, mean decreases in lipid parameters from baseline to Week 24 of FTC/RPV/TDF therapy were larger in subjects with prior LPV/r use at study entry compared with those without prior LPV/r use.

At study entry, 11.7% of subjects in the randomized FTC/RPV/TDF group and 18.2% of subjects in the SBR group reported use of a lipid-modifying agent. Few subjects (≤ 2.8% in each treatment group) added or modified the use of lipid-modifying agents during the study. When the mean values and mean changes from baseline in fasting glucose and lipid parameters were analyzed excluding subjects who started/modified lipid-lowering agents during the study, results were very similar to those described above for the analyses including these subjects.

**Table 92. Complera/Eviplera Study: GS-US-264-0106: Mean Value and Mean Change from Baseline in Fasting Lipid Parameters (Safety Analysis Set)**

| Treatment Group | FTC/ RPV/ TDF (N = 317)[a] | SBR (N = 159)[b] | Delayed Switch to FTC/ RPV/ TDF (N = 152)[c] | Total FTC/ RPV/ TDF (N = 469)[d] |
|---|---|---|---|---|
| **Fasting Serum Lipid Parameters** | | | | |
| **Fasting Total Cholesterol (mg/dL)** | | | | |
| Baseline, Mean (SD) | 192 (41.8) | 194 (36.5) | 193 (36.7) | 192 (40.1) |
| Week 24, Mean (SD) | 166 (33.7) | 193 (36.8) | 168 (30.2) | 167 (32.6) |
| Change from baseline to Week 24, Mean (SD) | -25 (30.2) | -1 (25.9) | -24 (32.0) | -25 (30.8) |
| p-value[e,f] | **< 0.001** | | | |
| Week 48, Mean (SD) | 168 (33.2) | | | 168 (33.2) |
| Change from baseline to Week 48, Mean (SD) | -24 (32.9) | | | -24 (32.9) |
| **Fasting HDL cholesterol (mg/dL)** | | | | |
| Baseline, Mean (SD) | 53 (15.9) | 50 (12.0) | 49 (12.1) | 52 (14.9) |
| Week 24, Mean (SD) | 49 (13.9) | 48 (12.3) | 47 (11.8) | 49 (13.3) |
| Change from baseline to Week 24, Mean (SD) | -4 (10.3) | -1 (8.2) | -2 (8.0) | -3 (9.6) |
| p-value[e,g] | **< 0.001** | | | |
| Week 48, Mean (SD) | 51 (14.8) | | | 51 (14.8) |
| Change from baseline to Week 48, Mean (SD) | -2 (11.6) | | | -2 (11.6) |
| **Fasting Direct LDL Cholesterol (mg/dL)** | | | | |
| Baseline, Mean (SD) | 121 (35.1) | 124 (31.3) | 123 (31.1) | 122 (33.8) |
| Week 24, Mean (SD) | 104 (30.0) | 123 (31.1) | 108 (27.0) | 105 (29.1) |
| Change from baseline to Week 24, Mean (SD) | -16 (25.6) | 0 (23.7) | -14 (26.8) | -16 (26.0) |
| p-value[e] | **< 0.001** | | | |
| Week 48, Mean (SD) | 106 (30.6) | | | 106 (30.6) |
| Change from baseline to Week 48, Mean (SD) | -16 (27.1) | | | -16 (27.1) |
| **Fasting Triglycerides (mg/dL)** | | | | |
| Baseline, Mean (SD) | 163 (136.2) | 173 (107.9) | 184 (163.2) | 170 (146.1) |
| Week 24, Mean (SD) | 111 (93.2) | 185 (165.7) | 108 (51.8) | 110 (81.9) |
| Change from baseline to Week 24, Mean (SD) | -53 (110.1) | 3 (100.1) | -80 (141.1) | -62 (122.0) |
| p-value[e] | **< 0.001** | | | |
| Week 48, Mean (SD) | 101 (54.1) | | | 101 (54.1) |
| Change from baseline to Week 48, Mean (SD) | -64 (126.4) | | | -64 (126.4) |

| Treatment Group | FTC/ RPV/ TDF (N = 317)[a] | SBR (N = 159)[b] | Delayed Switch to FTC/ RPV/ TDF (N = 152)[c] | Total FTC/ RPV/ TDF (N = 469)[d] |
|---|---|---|---|---|
| **Ratio of Fasting Total Cholesterol Over HDL Cholesterol** | | | | |
| Baseline, Mean (SD) | 3.86 (1.250) | 4.08 (1.111) | 4.28 (1.737) | 4.00 (1.445) |
| Week 24, Mean (SD) | 3.57 (1.185) | 4.31 (1.761) | 3.78 (1.023) | 3.64 (1.137) |
| Change from baseline to Week 24, Mean (SD) | -0.27 (0.913) | 0.08 (0.771) | -0.43 (0.941) | -0.32 (0.924) |
| p-value[e] | **< 0.001** | | | |
| Week 48, Mean (SD) | 3.50 (1.084) | | | 3.50 (1.084) |
| Change from baseline to Week 48, Mean (SD) | -0.35 (0.976) | | | -0.35 (0.976) |

Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.

a For fasting total cholesterol, HDL cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, N = 296 at baseline; N = 286 at Week 24; N = 269 for the change from baseline to Week 24; N = 282 at Week 48; and N = 265 for the change from baseline to Week 48. For fasting direct LDL cholesterol, N = 297 at baseline; N = 286 at Week 24; N = 270 for the change from baseline to Week 24; N = 282 at Week 48; and N = 265 for the change from baseline to Week 48.

b For fasting total cholesterol, HDL cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, N = 146 at baseline; N = 146 at Week 24, and N = 134 for the change from baseline to Week 24. For fasting direct LDL cholesterol, N = 146 at baseline; N = 145 at Week 24; and N = 134 for the change from baseline to Week 24.

c For fasting total cholesterol, direct LDL cholesterol, HDL cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, N = 152 at baseline; N = 139 at Week 24, and N = 139 for the change from baseline to Week 24.

d For fasting total cholesterol, HDL cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol, N = 448 at baseline; N = 425 at Week 24; N = 408 for the change from baseline to Week 24; N = 282 at Week 48; and N = 265 for the change from baseline to Week 48. For fasting direct LDL cholesterol, N = 449 at baseline; N = 425 at Week 24; N = 409 for the change from baseline to Week 24; N = 282 at Week 48; and N = 265 for the change from baseline to Week 48.

e P-value for comparison between FTC/RPV/TDF and SBR is from analysis of variance (ANOVA) of change from baseline at Week 24 with baseline stratification on LPV/r and treatment as fixed effects. Treatment by stratification interaction term was included in the model if significant.

f The interaction between stratification factor (LPV/r or not) and treatment was significant (p = 0.035) and therefore kept in the ANOVA model. P-value for stratification was equal to 0.002.

g The interaction between stratification factor (LPV/r or not) and treatment was significant (p = 0.039) and therefore kept in the ANOVA model. P-value for stratification was equal to 0.14.

Source: GS-US-264-0106 Week 48 CSR, Section 15.1, Tables 5.4.2–5.4.6

*Categorical Analysis of Fasting Lipid Parameters*

Similar results were obtained in categorical analyses of lipid parameters using categories consistent with the NCEP recommendations and World Health Organization (WHO) criteria for fasting lipid parameters. Consistent with the NCEP recommendations and WHO criteria, fasting lipid parameters were categorized using the following categories: < 200, 200 to < 240, ≥ 240 mg/dL for total cholesterol; < 100, 100 to < 130, 130 to < 160, 160 to < 190, and ≥ 190 mg/dL for LDL; < 40, 40 to < 60, ≥ 60 mg/dL for HDL; < 150, 150 to < 200, 200 to < 500, and ≥ 500 mg/dL for triglycerides; and < 3.5, 3.5 to < 4.4, 4.4 to < 5, and ≥ 5 for the ratio of total cholesterol over HDL {19575}. Treatment group differences were analyzed between the randomized FTC/RPV/TDF group and the SBR group through Week 24, stratified by LPV/r use at baseline.

At baseline, the percentages of subjects in each fasting lipid parameter category were similar between the FTC/RPV/TDF and SBR groups. By Week 12, the percentages of subjects with

target (optimal) fasting total cholesterol levels (< 200 mg/dL), direct LDL levels (< 100 mg/dL), triglycerides (< 150 mg/dL), and ratios of total cholesterol to HDL cholesterol (< 3.5) were increased in the FTC/RPV/TDF group compared with the SBR group. The percentages of subjects in these target (optimal) fasting lipid categories at Week 12 in the FTC/RPV/TDF and SBR groups were as follows: 86.6% vs. 60.1% for total cholesterol; 47.8% vs. 24.8% for direct LDL; 87.6% vs. 47.3% for triglycerides; and 57.9% vs. 31.1% for the ratio of total cholesterol to HDL. Similar results were observed at Week 24. Overall differences between the FTC/RPV/TDF and SBR groups in the categorical analyses of fasting total cholesterol, direct LDL, triglycerides, and the ratio of total cholesterol to HDL cholesterol (in favor of an improved lipid profile for the FTC/RPV/TDF group) were statistically significant at Weeks 12 and 24 ($p < 0.001$). The increase in the percentage of subjects with desirable total cholesterol levels observed at Weeks 12 and 24 in the randomized FTC/RPV/TDF group were generally maintained through Week 48 of therapy. After subjects in the SBR group switched to FTC/RPV/TDF therapy at Week 24, similar fasting total cholesterol category results were observed in the Delayed Switch group over 24 weeks of FTC/RPV/TDF therapy as were observed during the first 24 weeks of therapy in the randomized FTC/RPV/TDF group described above.

Similar trends were observed in categorical analyses of fasting total cholesterol, direct LDL, and triglycerides when subgroups of subjects with prior LPV/r use at study entry and those without prior LPV/r use were analyzed. The distribution of subjects across the ratio of fasting total cholesterol:HDL categories in the analysis of subjects with prior LPV/r use at study entry was significantly different between the FTC/RPV/TDF and the SBR groups at baseline ($p = 0.003$). However, a similar trend toward an improved profile for the ratio of fasting total cholesterol:HDL categories was observed for the FTC/RPV/TDF group in both subjects with prior LPV/r use at study entry and those without prior LPV/r use.

In the overall analysis and when subjects were stratified by LPV/r use at baseline, no significant differences in the distribution of subjects across the fasting HDL categories were observed at Weeks 12 and 24 between the FTC/RPV/TDF and SBR groups.

Results of sensitivity analyses of fasting lipid parameters excluding subjects who started/modified lipid-lowering agents during the study were similar to the overall analyses described above.

In summary, switching to the FTC/RPV/TDF STR resulted in improvements in fasting lipids, including total cholesterol, direct LDL, triglycerides, and the ratio of total cholesterol to HDL cholesterol as early as 12 weeks after initiating therapy, and this effect was maintained through up to 48 weeks of therapy. A greater decrease in HDL cholesterol levels from baseline to Week 24 was observed in the FTC/RPV/TDF STR group compared with the SBR group; however, no significant differences in the distribution of subjects across the fasting HDL categories were observed at Weeks 12 and 24 between the FTC/RPV/TDF and SBR groups.

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Detailed information on vital signs, physical findings, and other observations related to safety may be found in the respective CSRs for each study. Electrocardiogram parameters are presented in Section 2.1.9.5.

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

### 5.1.1. Summary of Intrinsic Factors

The safety of FTC/RPV/TAF as assessed by reported AEs and laboratory test abnormalities associated with treatment with E/C/F/TAF and RPV+FTC/TDF, were not affected by sex, age, race, HIV-1 RNA level, CD4 count, prior treatment regimen, or region.

Pharmacokinetic (PK) and relevant safety data support administration of FTC/RPV/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min). No additional measures outside of standard clinical practice guidelines for routine monitoring renal safety in subjects with mild to moderate renal impairment are indicated.

Pharmacokinetic and relevant safety data support administration of FTC/RPV/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class A or B). The PK of FTC/RPV/TAF has not been studied in subjects with hepatic impairment. Pharmacokintic data suggest that no dose adjustment of TMC278 is needed in subjects with mild or moderate hepatic impairment.

FTC has not been studied in hepatically impaired subjects, but renal excretion of unchanged drug is the major route of elimination of FTC with metabolism representing a minor pathway for the elimination (< 13% of oral dose). Therefore, in patients with various degrees of hepatic dysfunction, little change in FTC clearance is expected.

### 5.1.2. Sex

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in males and females for both treatment groups (E/C/F/TAF: male 90.2%, 661 of 733 subjects; female 88.0%, 117 of 133 subjects; STB: male 90.8%, 672 of 740 subjects; female 86.6%, 110 of 127 subjects) (E/C/F/TAF ISS, Table 8.2). Individual AEs were generally similar in males and females for both treatment groups.

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects experiencing any AE were comparable in males and females for both treatment groups (E/C/F/TAF: male 80.3%, 687 of 856 subjects; female 74.8%, 77 of 103 subjects; FTC/TDF+3rd Agent: male 76.8%, 328 of 427 subjects; female 80.0%, 40 of 50 subjects).

In the RPV group in the Phase 3 trials C209 and C215, no obvious differences in the incidence of treatment-related AEs of at least Grade 2 were reported between male subjects (18.1%) and female subjects (14.3%), in AEs leading to permanent discontinuation (6.5% in female subjects and 3.3% in male subjects), or in the incidence of rash events (grouped term) (7.7% in female subjects and 12.7% in male subjects). Similarly in the control group, no gender difference

was observed for treatment-related AEs of at least Grade 2 (35.0% and 32.6%, respectively) and AEs leading to permanent discontinuation (9.2% and 8.3%, respectively). In RPV-treated subjects, psychiatric events of interest and hepatic events of interest were reported at a higher incidence in male subjects (29.5% and 8.9%, respectively) than in female subjects (22.0% and 1.8%, respectively). Endocrine events of interest were reported at a higher incidence in female subjects (16.1%) than in male subjects (4.8%). Comparable gender differences in the incidence of psychiatric and endocrine events of interest were also seen in the control group. There was a comparable incidence of rash events in female subjects (27.6%) and male subjects (25.8%) and of hepatic events of interest (6.7% vs 8.7%, respectively).

No differences with regards to laboratory parameters (except in pancreatic amylase which was more common in male subjects than female subjects in the RPV group [9.7% vs 2.4%]) and ECG parameters were observed between male and female subjects.

5.1.2.1. TAF

**TAF**

Sex did not have an effect on TAF exposures in subjects and was not a statistically or clinically relevant covariate based on population PK analyses (m2.7.2, Section 3.3.2.6.1).

**TFV**

Based on covariate analyses, a statistically significant effect of sex on TFV PK parameters was observed. However, the range of TFV exposure across males and females was comparable. As such, the observed relationship between sex and TFV exposure is not considered to be clinically relevant.

5.1.2.2. RPV

Gender did have a statistically significant effect on the pharmacokinetics of TMC278 (m2.7.2, Section 3.3.2.6.2). In a multivariate analysis including trial, region, gender and race as factors, the effect of gender was still statistically significant. This resulted in a higher mean exposure in females (18%) compared to males. There is however a large overlap in the range of exposures between the different subgroups and these differences are not considered to be of clinical relevance. The observed differences are likely, at least in part, explained by the lower average bodyweight in females compared to males, as indicated by the absence of a significant effect of gender on CL/F corrected for bodyweight (CL/F/kg).

Also in the 48 week covariate analysis of the pooled Phase 3 pharmacokinetic data, a statistically significant effect of gender on the CL/F of TMC278 was observed. This covariate effect however appeared to have no impact on the overall inter-individual variability and had only a minor effect on explaining the difference between the extremes of the covariates. The covariate-induced difference in CL/F for gender was therefore considered not to be of clinical relevance and was not retained in the final population pharmacokinetic model.

In healthy subjects, the difference in pharmacokinetic parameters between males and females has not been systematically evaluated. For most of the Phase 1 trials, the trial population consisted largely of male subjects, except for the QT/QTc trials, where approximately 50% of subjects were female. No notable differences between males and females were observed in the mean pharmacokinetic profile of TMC278 in healthy subjects in trial C152 (25 mg once daily). However, in trials TMC278-TiDP6-C151 (C151; 25 mg once daily) and TMC278-TiDP6-C131 (C131; 75 and 300 mg once daily), the mean plasma concentrations at steady state were somewhat higher for females compared to males.

5.1.2.3. FTC

For FTC, there were no major differences with respect to range and distribution of AUC values between males and females (m2.7.2, Section 3.3.2.6.3). The 16% higher mean AUC and the ~20% higher $C_{max}$ in female subjects as compared with males are not considered clinically relevant. In addition, all $C_{max}$ data points in female subjects were within the $C_{max}$ data range of male subjects. There were no major differences in the overall range and distribution of $t_{1/2}$ values between male and female subjects. However, female subjects tended to have a shorter mean or median $t_{1/2}$ than male subjects by 12% or 17%.

### 5.1.3. Age

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects with any AE were comparable in subjects < 50 and ≥ 50 years in the E/C/F/TAF group (< 50 years 90.0%, 699 of 777 subjects; ≥ 50 years 88.8%, 79 of 89 subjects) and the STB group (< 50 years 89.8%, 676 of 753 subjects; ≥ 50 years 93.0%, 106 of 114 subjects) (E/C/F/TAF ISS, Table 8.1). In a pooled analysis of subjects aged ≥ 65 years in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102, all 4 subjects in the E/C/F/TAF group and 9 subjects (90%) in the STB group had at least 1 AE (E/C/F/TAF ISS, Table Req6744.2). One subject in each group (E/C/F/TAF 25%; STB 10%) had a Grade 3 or 4 AE; 1 subject (25%) in the E/C/F/TAF group and 2 subjects (20%) in the STB group had an SAE. No subject aged ≥ 65 years died or had any AE leading to study drug discontinuation.

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects with any AE were comparable in subjects < 50 and ≥ 50 years in the E/C/F/TAF group (< 50 years 79.2%, 610 of 770 subjects; ≥ 50 years 81.5%, 154 of 189 subjects) and the FTC/TDF+3rd Agent group (< 50 years 78.3%, 292 of 373 subjects; ≥ 50 years 73.1%, 76 of 104 subjects). In the subset of 19 subjects aged ≥ 65 years, at least 1 AE was reported in 11 subjects (91.7%) in the E/C/F/TAF group and 5 subjects (71.4%) in the FTC/TDF+3rd Agent group (E/C/F/TAF ISS, Table Req6758.2.2). No subject aged ≥ 65 years died or had an SAEs. In the E/C/F/TAF group, no subject had a Grade 3 or 4 AE or an AE that led to study drug discontinuation. In the FTC/TDF+3rd Agent group, 1 subject (14.3%) had a Grade 3 or 4 AE, and 1 subject (14.3%) had an AE that led to discontinuation of study drugs.

In E/C/F/TAF Study GS-US-292-0112, at least 1 AE was reported in 86.4% of subjects (n = 209: 67 [83.8%] with baseline $eGFR_{CG}$ < 50 mL/min and 142 [87.7%] with baseline $eGFR_{CG}$ ≥ 50 mL/min). In the subset of 63 subjects aged ≥ 65 years, at least 1 AE was reported

in 92.1% of subjects (22 [88.0%] with baseline $eGFR_{CG}$ < 50 mL/min and 36 [94.7%] with baseline $eGFR_{CG}$ ≥ 50 mL/min) (E/C/F/TAF ISS, Table Req6756.11).

In the adolescent E/C/F/TAF Study GS-US-292-0106, at least 1 AE was reported in 81.3% of subjects (39 of 48 subjects).

In the RPV Phase 3 trials C209 and C215, the incidence of SAEs was higher in the older subjects compared with younger subjects, both for RPV (24.2% vs 8.7%, respectively) and control (22.2% vs 9.9%, respectively). In the RPV group, the incidence of treatment-related AEs of at least Grade 2 was higher in subjects aged < 55 years (17.8%) than in subjects aged ≥ 55 years (6.1%), whereas in the control group the converse was observed (32.7% in subjects aged < 55 years and 44.4% in subjects aged ≥ 55 years). In the RPV group, skin events of interest and rash (grouped term) events were seen in a greater proportion of subjects aged ≥ 55 years (30.3% and 18.2%, respectively) than subjects aged < 55 years (17.9% and 11.2%, respectively). In the control group, skin events of interest were observed at a similar incidence in older and younger subjects (33.3% vs 30.5%, respectively), although rash events were seen at a higher incidence in younger than older subjects (26.6% and 18.5%, respectively), although since the number of subjects ≥ 55 years is low this observation should be treated with caution.

5.1.3.1. TAF

**TAF**

Age did not have an effect on TAF exposures in subjects and was not a statistically or clinically relevant covariate based on population PK analyses (m2.7.2, Section 3.3.2.2.1).

**TFV**

As age is often correlated with renal function and TFV is primarily renally eliminated, an effect of age on TFV exposure was expected; however, age was not found to be a statistically significant covariate after adjusting for $eGFR_{CG}$. Moreover, this age-dependent exposure difference was not considered clinically relevant because TFV exposure in subjects ≥ 55 years of age receiving E/C/F/TAF was at least 80% lower than TFV exposure observed following STB administration.

5.1.3.2. RPV

Age did not have a statistically significant effect on the exposure to TMC278 in HIV-1 infected subjects in the Phase 3 trials C209 and C215 (m2.7.2, Section 3.3.2.2.2). This was confirmed in the covariate analysis of the pooled Phase 3 pharmacokinetic data, where age was not retained as a significant covariate affecting the CL/F of TMC278.

5.1.3.3. FTC

For FTC PK, there were no relevant differences with respect to range and distribution of AUC values between age groups examined (m2.7.2, Section 3.3.2.2.3). Subjects > 40 years had slightly higher (< 10%) mean/median AUC and $C_{max}$ values than subjects ≤ 40 years of age.

There were no major differences in the overall range and distribution of $t_{1/2}$ values between the 2 age groups. However, subjects > 40 years of age had a longer mean or median $t_{1/2}$ than subjects ≤ 40 years by 26% or 30%.

### 5.1.4. Race

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in black and nonblack subjects for both treatment groups (E/C/F/TAF: black 90.6%, 202 of 223 subjects; nonblack 89.6%, 576 of 643 subjects; STB: black 91.5%, 195 of 213 subjects; nonblack 89.8%, 587 of 654 subjects) (E/C/F/TAF ISS, Table 8.3).

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects experiencing any AE were comparable in black and nonblack subjects for both treatment groups (E/C/F/TAF: black 77.5%, 131 of 169 subjects; nonblack 80.2%, 632 of 788 subjects; FTC/TDF+3rd Agent: black 72.5%, 74 of 102 subjects; nonblack 78.3%, 293 of 374 subjects).

In E/C/F/TAF Study GS-US-292-0108, 6 Japanese subjects (60.0%) and 9 white subjects (90.0%) experienced at least 1 AE. No significant differences in safety parameters between Japanese and white subjects were noted.

Overall, RPV was generally safe and well-tolerated in each racial subgroup in the Phase 3 trials C209 and C215. Comparisons should be treated with caution due to the small number of subjects in the Asian subgroup relative to the other racial subgroups. There were no apparent differences in the incidence of AEs and laboratory abnormalities between the 2 largest racial subgroups, except in neurologic and psychiatric events of interest, which were reported at a greater incidence in the White subgroup (32.9%) than in the Asian (20.5%) or Black/African American (17.0%) subgroup. Endocrine events of interest were reported at a higher incidence in the Asian subgroup (12.8%) than in the Black/African American (9.1%) or White (5.5%) subgroup. The incidence of SAEs, AEs leading to discontinuation, and treatment-related AEs of at least Grade 2 was lower in the Asian subgroup compared with the Black/African American or White subgroup.

With the exception of decreased WBC count, the incidence of most graded laboratory abnormalities was lower in the Asian subgroup. Decreased WBC count was reported for 12.8% RPV-treated subjects in the Asian subgroup compared with 1.8% and 2.1% in the Black/African American and White subgroup, respectively.

The subgroup analysis by race of the ECG parameters did not show any relevant differences between the different racial subgroups.

5.1.4.1. TAF

**TAF**

Using population PK modeling, race did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically significant or clinically relevant covariate (m2.7.2, Section 3.3.2.4.1).

**TFV**

Based on covariate analyses, a statistically significant effect of race (black versus nonblack) on TFV PK parameters was observed. However, the range of TFV exposure across races was comparable and overall > 80% lower than TFV exposure observed following STB administration. As such, the observed relationship between race and TFV exposure is not considered clinically relevant.

5.1.4.2. RPV

Race did have a statistically significant effect on the pharmacokinetics of TMC278 (m2.7.2, Section 3.3.2.4.2). In a multivariate analysis including trial, region, gender and race as factors, the effect of race was still statistically significant. This resulted in a higher mean exposure in Asians (19%) compared to other races. There is however a large overlap in the range of exposures between the different subgroups and these differences are not considered to be of clinical relevance. The observed differences are likely, at least in part, explained by the lower average bodyweight in Asians compared to other races, as indicated by the absence of a significant effect of race on CL/F corrected for bodyweight (CL/F/kg).

Also in the 48 week covariate analysis of the pooled Phase 3 pharmacokinetic data, a statistically significant effect of race on the CL/F of TMC278 was observed. This covariate effect however appeared to have no impact on the overall inter-individual variability and had only a minor effect on explaining the difference between the extremes of the covariates. The covariate-induced difference in CL/F for race was therefore considered not to be of clinical relevance and was not retained in the final population pharmacokinetic model.

5.1.4.3. FTC

There were no major differences in the overall range and distribution or in the mean/median values for any of the key FTC PK parameter estimates (AUC, $C_{max}$ and $t_{1/2}$) between the Caucasian and non-Caucasian groups (m2.7.2, Section 3.3.2.4.3)

### 5.1.5. HIV-1 RNA Stratum at Baseline

In in ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in subjects with baseline HIV-1 RNA level ≤ 100,000 copies/mL and > 100,000 copies/mL for both treatment groups (E/C/F/TAF: HIV-1 RNA level ≤ 100,000 copies/mL 89.6%, 600 of 670 subjects; > 100,000 copies/mL 90.8%, 178 of 196 subjects; STB: HIV-1 RNA level ≤ 100,000 copies/mL

89.6%, 602 of 672 subjects; > 100,000 copies/mL 92.3%, 180 of 195 subjects) (E/C/F/TAF ISS, Table 8.4).

### 5.1.6. CD4 Cell Count at Baseline

5.1.6.1. E/C/F/TAF

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in subjects with baseline CD4 count < 200 cells/μL and ≥ 200 cells/μL for both treatment groups (E/C/F/TAF: CD4 count < 200/μL 90.2%, 101 of 112 subjects; ≥ 200/μL 89.8%, 676 of 753 subjects; STB: CD4 count < 200/μL 88.0%, 103 of 117 subjects; ≥ 200/μL 90.5%, 679 of 750 subjects) (E/C/F/TAF ISS, Table 8.5).

5.1.6.2. RPV

In the RPV group, no obvious differences were observed in the incidence of AEs in any of the subgroups, except in neuropsychiatric events of interest, driven by psychiatric events of interest, with the greatest incidence observed with CD4 cell counts (absolute) of > 350 cells/μL (50.0%).

### 5.1.7. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

5.1.7.1. TAF

The safety endpoints for the PK/PD analyses based on population PK estimates were:

- Presence or absence of diarrhea, nausea, vomiting, and gastrointestinal (GI) and abdominal pains (excluding oral and throat) (which included: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, and GI pain)
- Percent change from baseline at Week 48 in hip and spine bone mineral density (BMD)
- Maximum increase from baseline through Week 48 in serum creatinine
- Change from baseline at Week 48 for select fasted lipids (total cholesterol, low-density lipoprotein, and high-density lipoprotein)

Analyses were performed between the exposure parameters (ie, $AUC_{tau}$ and $C_{max}$) of TAF or TFV (estimated from population PK modeling for TAF or TFV).

The relationships between plasma TAF and TFV concentrations and ΔΔQTcF were evaluated in a thorough QT/QTc study of TAF single agent.

TAF exposure was comparable regardless of the presence or absence of diarrhea and/or GI/abdominal pain, and no relevant exposure-AE trends were observed with these AEs. TAF exposure was generally comparable in the presence or absence of nausea and/or vomiting, but logistic regression analysis showed a trend between the highest TAF exposure and the presence

of these AEs (nausea correlated with the highest 4% of TAF exposure; vomiting correlated with the highest 19% of TAF exposure). No trend was observed between exposure and severity. The overall incidence of nausea and vomiting was similar between treatment groups in the pivotal Phase 3 studies (E/C/F/TAF ISS, Table 7).

Percentage change from baseline in BMD at the hip and at the spine at Week 48 were also key safety endpoints of Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TAF exposure quartiles and changes in BMD at the hip and spine were evaluated. Across all TAF $AUC_{tau}$ quartiles, percentage change from baseline at the hip and at the spine at Week 48 in BMD were comparable; no trends in exposure changes in BMD were noted.

The change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TAF exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated. Across all TAF $AUC_{tau}$ quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in serum creatinine were noted.

A linear mixed-effect model of the relationship between plasma concentrations of TAF and ΔΔQTcF suggest there is no statistically significant or pharmacologically meaningful association between TAF plasma concentration and ΔΔQTcF interval (Study GS-US-120-0107).

**TFV**

For diarrhea, GI/abdominal pain, nausea, and vomiting, TFV exposure was comparable regardless of the presence or absence of either of those symptoms, and no exposure-AE trends were observed with these AEs.

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were also key safety endpoints in Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TFV exposure quartiles and changes in BMD at the hip and spine were evaluated. The percentage change from baseline at Week 48 was comparable across all TFV $AUC_{tau}$ quartiles for both hip and spine BMD; no exposure-changes in BMD trends were noted.

Change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TFV exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated. Maximum increase from baseline in serum creatinine was comparable across TFV AUCtau quartiles; no exposure changes in serum creatinine trends were noted.

A linear mixed-effect model of the relationship between plasma concentrations of TFV and ΔΔQTcF suggest there is no pharmacologically meaningful association between plasma concentrations of TFV and ΔΔQTcF, ΔQTcF, or raw QTcF (Study GS-US-120-0107).

Further details are provided in m2.7.2, Section 3.4.2.1.

### 5.1.7.2. RPV

No obvious relationship was seen between the exposure to TMC278 and the occurrence of AEs (i.e., rash, anemia, dizziness, headache, abnormal dreams, neuropsychiatric events, nervous system disorders, psychiatric disorders, blood and lymphatic system disorders, gastrointestinal disorders, and QTc-prolongation related events) in the Phase 3 trials C209 and C215 (m2.7.2, Section 3.4.2.2).

No relationship was seen between the exposure to TMC278 and clinically relevant changes in laboratory parameters of interest in the Phase 3 trials C209 and C215.

A pilot trial (C151) of TMC278 indicated that there is no clinically relevant effect of TMC278 25 mg once daily on QTcF interval. In HIV-1 infected subjects treated with TMC278 at doses of 25, 75, and 150 mg once daily in the dose-finding Phase 2b trial C204, a gradual increase in QTcF interval over time was observed. In the Phase 3 trials C209 and C215, there was also a gradual increase over time in the mean QTcF interval. This was also apparent in the control group, and there was no notable difference between the TMC278 and control group at any time point during the 96-week treatment period (m2.7.2, Section 3.4.2.2).

During clinical use in HIV-1 infected subjects, plasma concentrations of TMC278 could be (temporarily) enhanced under certain circumstances, e.g., by interaction with co-medications that inhibit CYP3A enzymes. Therefore, to explore the increase in TMC278 exposure ($C_{max}$) compared to the exposure obtained with TMC278 25 mg once daily that can still be assumed to have no discernible effect on the QTcF interval (i.e., upper limit of the 90% CI of the mean QTcF interval prolongation < 10 ms), simulations were performed to assess the effect of increase in TMC278 exposure on the upper limit of the 2-sided 90% CI of the mean QTcF interval prolongation (QT/QTc trials C131 and C152). In conclusion, with these analyses, it was determined that there is a probability of 80% that the upper limit of the 2-sided 90% CI of the mean change in QTcF interval remains below 10 ms at an increase in exposure ($C_{max}$) of 85% (1.85-fold) compared to the $C_{max}$ at the 25 mg once daily dose, taking into account the variability in the pharmacokinetics (m2.7.2, Section 3.4.2.2).

The impact of possible factors (e.g., drug-drug interactions) that would increase the exposure to TMC278 (based on $C_{max}$) by no more than 85% (1.85-fold) is not expected to be of clinical relevance or cause safety concerns, and would therefore not result in the need for dose adjustment.

### 5.1.7.3. FTC

The PK-PD analyses of the FTC exposure safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2 and Phase 3 studies using FTC exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea (m2.7.2, Section 3.4.2.3). The relationship between FTC exposure quartiles and changes in renal laboratory parameters was also evaluated.

FTC exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed. As observed for the other agents, across all FTC

$AUC_{tau}$ quartiles, the maximum increase from baseline in serum creatinine was comparable, and no trends in exposure-changes in laboratory parameters were noted. Importantly, the range of FTC exposures explored in these PK/PD analyses covered the individual FTC exposures observed in the renally impaired, HIV-infected subjects with $eGFR_{CG} < 50$ mL/min receiving E/C/F/TAF in Phase 3 Study GS-US-292-0112. Moreover, as demonstrated in Study GS-US-292-0112, subjects with $eGFR_{CG} < 50$ mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG} \geq 50$ mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

### 5.1.8. Renal Impairment

Pharmacokinetic data, and relevant safety data, support administration of FTC/RPV/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) (m2.7.2, Section 3.3.2.1).

#### 5.1.8.1. TAF

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, baseline eGFR was not a statistically significant or clinically relevant covariate influencing TAF PK. As expected due to renal elimination, FTC PK parameters were higher in subjects with mild to moderate renal impairment compared with those having normal renal function in the Phase 2 and 3 E/C/F/TAF studies in ART naive subjects. However, the FTC PK parameters were comparable to the mean FTC PK parameters achieved in subjects with mild renal impairment not requiring dose adjustment {23270}, {30162}. Moreover, subjects with $eGFR_{CG} < 50$ mL/min receiving E/C/F/TAF did not have a different safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min.

No additional measures outside of standard clinical practice guidelines for routine monitoring renal safety in subjects with mild to moderate renal impairment are indicated.

**TAF**

In the Phase 1 Study GS-US-120-0108, the PK of TAF and TFV was analyzed in non−HIV-infected subjects with severe renal impairment (defined as subjects with $eGFR_{CG}$ between 15 mL/min and 29 mL/min [inclusive], not on dialysis) and in age- and sex-matched non–HIV-infected subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min) following a single dose of TAF. Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure (as assessed by $AUC_{inf}$) relative to age- and sex-matched subjects with normal renal function. These data supported the conduct of a clinical study to evaluate the safety and efficacy of E/C/F/TAF in HIV-infected patients with mild to moderate renal impairment (Study GS-US-292-0112).

A Phase 3 PK substudy (n = 30) evaluating the PK of TAF following administration of E/C/F/TAF was performed in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min at screening, and showed mean (%CV) TAF and TFV exposures (AUC) of 254.2 (54.1) ng*h/mL (n = 29) (GS-US-292-0112). The TAF exposure was

numerically higher in subjects with baseline eGFRCG < 50 versus ≥ 50 mL/min. These Phase 3 data are also consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, baseline eGFR was not a statistically significant or clinically relevant covariate influencing TAF PK. Although TAF exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ ($30 \leq eGFR_{CG} < 60$ mL/min; mean [%CV] AUC 305.0 [112.5] ng•h/mL; $C_{max}$ 208.6 [53.0] ng/mL) relative to those with normal renal function (> 90 mL/min) the difference between those with moderate renal impairment and those with normal renal function was less than 50% (mean [%CV] AUC 210.4 [94.1] ng•h/mL; $C_{max}$158.9 [57.1] ng/mL).

**TFV**

Following a single dose of TAF, non–HIV-infected subjects with severe renal impairment in Study GS-US-120-0108 had a 6.05-fold mean increase in systemic TFV exposure (as assessed by $AUC_{inf}$) relative to age- and sex-matched non–HIV-infected subjects with normal renal function. The mean (%CV) TFV exposure observed in this study in subjects with severe renal impairment (2073.8 [47.1] ng*h/mL) was within or below the ranges of TFV plasma exposure observed in historical studies after administration of TDF 300 mg in both HIV-infected and non−HIV-infected subjects with normal renal function.

In the Phase 3 PK substudy (n = 30) of E/C/F/TAF in HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min (Study GS-US-292-0112) at screening, mean (%CV) TFV exposure (AUC) was 552.7 (32.0) ng*h/mL (n = 29) (Study GS-US-292-0112). The TFV exposure was numerically higher in subjects with baseline $eGFR_{CG} < 50$ versus ≥ 50 mL/min. These Phase 3 data are also consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses; this result was expected with TFV being primarily renally eliminated. Although TFV exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ relative to those with normal renal function, the TFV exposure observed in subjects with $eGFR_{CG} < 50$ mL/min was within or below the ranges of exposure observed in historical studies after administration of TDF 300 mg in both HIV-infected and non−HIV-infected subjects with normal renal function {26885}, {34210}.

5.1.8.2. RPV

In view of the negligible renal excretion of TMC278 (C119), a trial to investigate the exposure to TMC278 in subjects with renal impairment has not been conducted. In view of the negligible renal excretion of TMC278 (< 1%), no dose adjustment of RPV is required in patients with renal impairment (m2.7.2, Section 3.3.2.1.1.2).

A univariate analysis for the 96 week pooled Phase 3 data (trials C209 and C215;), evaluating the impact of different intrinsic factors on the PK parameters of TMC278, indicated that the factor of eGFR had no statistically significant effect on the exposure to TMC278 in HIV-1 infected subjects. This was confirmed in the covariate analysis of the pooled Phase 3

pharmacokinetic data, where eGFR was not retained as a significant covariate affecting the CL/F of TMC278.

5.1.8.3. FTC

Because renal excretion of the unchanged drug is the principal route of elimination for FTC, it is anticipated that the PK profiles of FTC in subjects with altered or deficient renal function may vary or deviate from those in subjects with normal renal function. Adult subjects with varying degrees of renal impairment (or insufficiency), as determined by $eGFR_{CG}$ values, were evaluated in Study FTC-107.

Study FTC-107 was an open-label, parallel group study with 6 subjects in each of the 5 groups with varying degrees of renal impairment as determined by $eGFR_{CG}$ values (> 80 mL/min as normal function; 50-80 mL/min as mild impairment; 30-49 mL/min as moderate impairment; < 30 mL/min as severe impairment; or functional anephric requiring hemodialysis).

The percentage of dose excreted as unchanged FTC in urine for the normal and mild renal impairment groups ($eGFR_{CG}$ 50-80 mL/min) was similar to that observed with healthy subjects (FTC-106) and HIV-infected subjects with normal renal function (FTC-101). In subjects with moderate and severe impairment ($eGFR_{CG}$ < 50 mL/min), the urinary recovery was lower (approximately 30%-50% of the dose) over a 72-hour collection period, primarily due to slower excretion of FTC by the impaired kidneys, which, in the absence of clinical experience of FTC in HIV-infected subjects with $eGFR_{CG}$ < 60 mL/min, led to a dose interval adjustment recommendation.

A Phase 3 efficacy and safety study was conducted to evaluate the effect of the E/C/F/TAF on renal parameters in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min (Study GS-US-292-0112). This study included an intensive PK substudy evaluating the PK of FTC following administration of E/C/F/TAF in subjects with $eGFR_{CG}$ of 30 to 69 mL/min (n = 30) and showed mean (%CV) FTC exposure AUC and $C_{max}$ of 20,968.6 (25.5) ng*h/mL and 2645.3 (24.7) ng/mL, respectively, which were in the range of exposures where dose modification was not warranted in FTC-107. Importantly, the mean FTC AUC and $C_{max}$ observed in GS-US-292-0112 subjects with $eGFR_{CG}$ of 30 to 69 mL/min were comparable with the AUC and $C_{max}$ of 19,900 (6.2) ng*h/mL and 3800 (2.3) ng/mL, respectively, from the Emtriva prescribing information for subjects with $eGFR_{CG}$ of 50 to 80 mL/min who do not require dose adjustment {23270}, {30162}. Subjects with $eGFR_{CG}$ < 50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG} \geq 50$ mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

The totality of these data supports the recommendation that FTC/RPV/TAF may be safely administered once daily without dose adjustment in patients with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min).

## 5.1.9. Hepatic Impairment

### 5.1.9.1. TAF

Pharmacokinetic and relevant safety data support administration of FTC/RPV/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate hepatic impairment (CPT Class A or B) (m2.7.2, Section 3.3.2.1.2.1).

The PK of TAF and its metabolite TFV was evaluated in non-HIV-infected subjects with mild or moderate hepatic impairment (CPT Class A or B) and in age- and sex-matched non–HIV-infected subjects with normal hepatic function following a single dose of TAF in Study GS-US-120-0114. The effect of severe hepatic impairment on the PK of TAF has not been studied.

**TAF**

The plasma exposure parameters of TAF were comparable ($AUC_{inf}$, $AUC_{last}$, and $C_{max}$ were 12.69%, 15.06%, and 18.70% higher, respectively) in non–HIV-infected subjects with moderate hepatic impairment relative to age- and sex-matched control subjects with normal hepatic function; the observed increases were not considered to be clinically relevant.

**TFV**

The plasma exposure parameters of TFV were comparable ($AUC_{inf}$, $AUC_{last}$, and $C_{max}$ were 10.84%, 10.69%, and 2.97% lower, respectively) in non–HIV-infected subjects with mild hepatic impairment relative to age- and sex-matched control subjects with normal hepatic function; the observed decreases were not considered to be clinically relevant. The plasma exposure parameters of TFV were comparable ($AUC_{inf}$, $AUC_{last}$, and $C_{max}$ were 2.78%, 4.45%, and 12.44% lower, respectively) in non–HIV-infected subjects with moderate hepatic impairment relative to age- and sex-matched control subjects with normal hepatic function; the observed decreases were not considered to be clinically relevant.

### 5.1.9.2. RPV

The pharmacokinetics of RPV as an individual agent were evaluated in a single-dose Phase I trial (C130) in which the short-term safety and tolerability of a TMC278 dose in 8 subjects with mild hepatic impairment (Child Pugh A) and 8 subjects with moderate hepatic impairment (Child Pugh B) was compared with that of healthy matched control subjects with normal hepatic function.

Over the course of this trial, AEs were most frequently reported in subjects with hepatic impairment. There were no deaths, AEs leading to discontinuation, or skin events of interest reported during the trial. Nervous system disorders were the most frequently experienced AEs, which were reported for 5 subjects. The majority of AEs were Grade 1 or 2 in severity and the only AE reported to be possibly related to TMC278 by the investigator that was experienced by > 1 subject across all panels was headache. No consistent or clinically relevant changes in mean

laboratory parameters were observed. There were no notable variations in ECG parameters or vital signs over time. Details can be found in the individual CRR (TMC278-C130-CRR).

No dose adjustment is required for subjects with mild or moderate hepatic impairment. TMC278 has not been investigated in subjects with severe hepatic impairment.

5.1.9.3. FTC

The PK of FTC has not been studied in hepatically impaired subjects. Renal excretion of unchanged drug is the major route of elimination of FTC in humans with metabolism representing a minor pathway for the elimination (< 13% of oral dose) (Study FTC-106). Therefore, in patients with various degrees of hepatic dysfunction, little change in FTC clearance is expected (m2.7.2, Section 3.3.2.1.2.3).

## 5.1.10. Coinfection with HIV-1 and Hepatitis B and/or Hepatitis C Virus

5.1.10.1. E/C/F/TAF

Subjects who were hepatitis C antibody positive were excluded from all Phase 2 and 3 studies of E/C/F/TAF. The exclusion criteria for Study GS-US-292-0104 were updated in Amendment 1 of the protocol to exclude subjects with positive HBV surface antigen. All of the other Phase 2 and Phase 3 studies of E/C/F/TAF excluded subjects with positive HBV surface antigen. In Study GS-US-292-0104, Subject [redacted] in the STB group tested positive for HBV surface antigen at screening and discontinued study drugs on Day 32 due an SAE of Grade 3 immune inflammatory syndrome due to HBV, which resulted in unblinding of study drug.

Subject [redacted] in the E/C/F/TAF group of Study GS-US-292-0104 had normal liver function tests (LFTs) at screening, and high AST (Grade 2) and ALT (Grade 3) at baseline (AST = 117 U/L, ALT = 237 U/L). AST returned to within the normal range on Day 18, and ALT was within the normal range by Day 26. On Day 84, ALT was again elevated (55 U/L, Grade 1). On Day 113, the subject had a nonserious AE of Grade 2 hepatitis C (ALT = 788 U/L, Grade 4; AST = 383 U/L, Grade 4) considered unrelated to the study drugs by the investigator. On Day 133 the subject tested positive for HCV antigen. On Day 181, the subject commenced treatment with subcutaneous pegylated interferon and oral ribavirin (treatment ongoing). By Day 253, all LFTs were within the normal range; however the event of hepatitis C was ongoing.

The PK of FTC was evaluated in a Phase 1 study in subjects with chronic HBV (Study FTCB-101). Based on the steady-state data from FTCB-101, FTC PK in HBV-infected subjects are generally similar to those determined previously in healthy subjects and in HIV-infected subjects.

Study GS-US-292-1249 is a Phase 3b, open-label study of E/C/F/TAF FDC in adult subjects who are coinfected with HIV-1 and hepatitis B. The study is ongoing.

No dose adjustment of E/C/F/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B).

5.1.10.2. RPV

In the Phase III pooled analysis, (Studies C209 and C215), approximately 9% of subjects were reported to be coinfected with HBV and/or C at baseline or on-treatment. As expected, in both treatment groups of Studies C209 and C215, hepatic events of interest and elevated hepatic parameters were observed at a higher incidence in subjects who were coinfected with HBV and/or HCV than in subjects who were not coinfected. The incidence of hepatic events of interest and the incidence of elevated hepatic laboratory parameters in coinfected subjects was comparable in both the TMC278 and control groups.

In Study C209, as expected, a greater proportion of TMC278-treated subjects with HBV and/or HCV coinfection experienced hepatic events of interest (27.8%) than subjects without coinfection (3.6%). These events were mostly abnormalities in AST and ALT reported in the SOC of investigations. Similar results were observed in the control group. As expected, in both treatment groups, hepatic events of interest were observed at a higher incidence in subjects who were coinfected with HBV and/or HCV than in subjects who were not coinfected. The incidence of hepatic events of interest in coinfected subjects was comparable in both the TMC278 and control groups.

In Study C215, review of Grade 2, 3, and 4 hepatic laboratory abnormalities for TMC278-treated subjects with and without HBV and/or HCV coinfection indicates that Grade 2, 3, and 4 increases in AST and ALT are seen at higher incidence in subjects with HBV and/or HCV coinfection (20.4% and 33.3%, respectively) than in subjects who are not coinfected (3.5% and 2.7%, respectively). Hyperbilirubinemia of at least Grade 2 was also seen at a higher incidence in subjects with HBV and/or HCV coinfection (7.4%) than in subjects who are not coinfected (2.7%). There was a higher incidence of Grade 2, 3, and 4 increases in AST and ALT on control than on TMC278 for both coinfected and noncoinfected subjects. On control, AST and ALT increases were seen for 18.2% and 28.8% of coinfected subjects and for 8.0% and 7.8% of noncoinfected subjects. As expected, in both treatment groups, elevated hepatic parameters were observed at a higher incidence in subjects who were coinfected with HBV and/or HCV than in subjects who were not coinfected. The incidence of elevated hepatic laboratory parameters in coinfected subjects was comparable in both the TMC278 and control groups.

## 5.2. Extrinsic Factors

### 5.2.1. Summary of Extrinsic Factors

### 5.2.2. Prior Treatment Regimen

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects with any AE were comparable in subjects who received prior treatment with STB (E/C/F/TAF 79.1%, 242 of 306 subjects; FTC/TDF+3rd Agent 77.1%, 118 of 153 subjects), ATR (E/C/F/TAF 82.1%, 206 of 251 subjects; FTC/TDF+3rd Agent 76.8%, 96 of 125 subjects), or ATV/boosted+TVD (E/C/F/TAF 78.6%, 316 of 402 subjects; FTC/TDF+3rd Agent 77.4%, 154 of 199 subjects).

### 5.2.3. Effect of Food

The effect of food on the absorption/bioavailability of FTC/RPV/TAF was evaluated in Study GS-US-366-1651, a randomized, open-label, single-dose, 2-period, crossover PK study of TAF, RPV, and FTC administered as the FTC/RPV/TAF FDC tablet (m2.7.1, Section 2.1.2).

#### 5.2.3.1. TAF

In Study GS-US-366-1651, when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed conditions compared with fasted conditions, TAF $AUC_{last}$ increased by 45% after moderate-fat food (mean TAF $AUC_{last}$: 325.1 and 223.8 h•ng/mL under fed, moderate-fat and fasted conditions, respectively) and TAF $AUC_{last}$ increased by 54% after high-calorie, high-fat food (mean TAF $AUC_{last}$: 311.7 and 201.1 h•ng/mL under fed, high-calorie, high-fat and fasted conditions, respectively). TAF $C_{max}$ decreased by 23% after moderate-fat food (mean TAF $C_{max}$: 306 and 386 ng/mL under fed, moderate-fat and fasted conditions, respectively) and TAF $C_{max}$ decreased by 31% after high-calorie, high-fat food (mean TAF $C_{max}$: 230 and 316 ng/mL under fed, high-calorie, high-fat and fasted conditions, respectively). There was also a delay in $T_{max}$ (increase from 0.5 hours under fasted conditions to 1.3 hours under moderate-fat conditions and to 1.5 hours under high-calorie, high-fat conditions).

The TAF exposures when the FTC/RPV/TAF tablet is administered with and without food fall within the wide range of safe and efficacious TAF exposure established in the Phase 3 E/C/F/TAF studies (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng•h/mL [55.6 to 526.1 ng•h/mL, 71.8%]). Therefore, the differences in TAF exposure when the FTC/RPV/TAF tablet is administered with food are not clinically relevant.

#### 5.2.3.2. RPV

In Study GS-US-366-1651, when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed conditions compared with fasted conditions, RPV $AUC_{inf}$ increased by 13% and 73% after moderate-fat and high-calorie, high-fat food, respectively. RPV $C_{max}$ increased by 39% and 107% when administered under moderate-fat and high-calorie, high-fat conditions, respectively, compared with fasted conditions. There was also a delay in median $T_{max}$ under moderate-fat conditions (increase from 3 hours under fasted conditions to 4 hours under moderate-fat conditions) and no change under high-calorie, high-fat conditions (4 hours for both fasted and high-calorie, high-fat conditions).

Bioequivalence of RPV exposure has been demonstrated under fed conditions between FTC/RPV/TAF and Edurant, a marketed product with clinical efficacy and safety established when administered under fed conditions {27873}, {29500}, {30163}, {30959}.

#### 5.2.3.3. FTC

In Study GS-US-366-1651, when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed conditions compared with fasted conditions, FTC $AUC_{inf}$ decreased by 9% and 12% after moderate-fat and high-calorie, high-fat food, respectively. FTC $C_{max}$ decreased by 24% and 26% when administered under moderate-fat and high-calorie, high-fat conditions,

respectively, compared with fasted conditions. There was also a delay in median $T_{max}$ (increase from 1.0 hour under fasted conditions to 2.0 hours under moderate-fat conditions and 2.0 hours under high-calorie, high-fat conditions). These findings are consistent with previous results {30162}, {23270}.

5.2.3.4. FTC/RPV/TAF

The results from Study GS-US-366-1651 are consistent with previous studies of TAF and FTC, supporting administration of these compounds without regard to food. However, bioequivalence of RPV exposure has been demonstrated under fed conditions been FTC/RPV/TAF and Edurant, a marketed producted with clinical efficacy and safety established when administered under fed conditions {27873}, {29500}, {30163}, {30959}. Therefore, the FTC/RPV/TAF FDC should be administered with food.

**5.2.4. Region**

5.2.4.1. F/TAF

In ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in subjects from the United States (US) and ex-US regions for both treatment groups (E/C/F/TAF: US 90.0%, 479 of 532 subjects; ex-US 89.5%, 299 of 334 subjects; STB: US 91.9%, 489 of 532 subjects; ex-US 87.5%, 293 of 335 subjects; E/C/F/TAF ISS, Table 8.6).

In virologically suppressed subjects in Study GS-US-292-0109, the percentages of subjects experiencing any AE were comparable in subjects from the US and ex-US regions for both treatment groups (E/C/F/TAF: US 79.9%, 518 of 648 subjects; ex-US 79.1%, 246 of 311 subjects; FTC/TDF+3rd Agent: US 75.3%, 238 of 316 subjects; ex-US 80.7%, 130 of 161 subjects).

5.2.4.2. RPV

The 2 Phase 3 trials C209 and C215 were conducted in 4 regions:

- Region 1: USA, Canada, Europe, Australia
- Region 2: Africa
- Region 3: Asia
- Region 4: Latin America

No analysis by region was performed.

## 5.3. Drug Interactions

### 5.3.1. TAF

**TAF**

The potential for TAF to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (AD-120-2003). The inhibitory activity of TAF with human liver microsomal CYP isoenzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 µM. The $IC_{50}$ values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 µM. TAF weakly inhibited CYP3A-mediated oxidation of midazolam (MDZ) or testosterone with $IC_{50}$ values of 7.6 and 7.4 µM, respectively.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A was assessed at TAF concentration at 50 µM (AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

Clinical evaluation of TAF as a CYP3A4 inhibitor or inducer (Study GS-US-120-1538;) showed no clinically relevant differences in MDZ PK relative to MDZ alone following coadministration of MDZ (oral or intravenous) and TAF; these data indicate that TAF does not exhibit CYP3A inhibition or induction activity, either presystemically or systemically.

TAF is transported by P-gp and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity (eg, COBI) may lead to changes in TAF bioavailability. Coadministration with COBI can lead to near maximal inhibition of P-gp, resulting in an increase in TAF exposure.

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inducers are not expected to have a relevant effect on TAF PK; however, most CYP inducers are also P-gp inducers, and coadministration with P-gp inducers may decrease the absorption of TAF. Coadministration with a moderate CYP3A and P-gp inducer (ie, EFV) resulted in slightly lower TAF exposure (14% to 22%), and coadministration with a weak CYP3A and P-gp inducer (ie, RPV) resulted in no change to TAF exposure. As such, minimal effect on TAF exposure is expected when administered as part of the FTC/RPV/TAF FDC.

Because TAF was found to be a substrate for hepatic transporters organic anion transporting polypeptide (OATP)1B1 and OATP1B3 (m2.7.2, Section 3.2.3.4), exposure to TAF may be affected by inhibitors of OATP1B1 and OATP1B3 or by genetic polymorphisms affecting their transport activities. The effects of differences in OATP1B1 and OATP1B3 activity are, however, not expected to be clinically relevant given the high passive permeability of TAF.

**TFV**

The potential for TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (V990172-104). TFV at 100 µM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

### 5.3.2. RPV

Overall, TMC278 at the dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of coadministered drugs. A total of 19 Phase I drug-drug interaction trials have been conducted to evaluate the effects of co-administering TMC278 with various classes of ARV and non-ARV drugs that are commonly used in the HIV-1 infected population. For details on established and theoretical drug interactions with TMC278 and for the dosage recommendations, refer m2.7.2, Section 3.3.3.2. Drug-drug interactions were evaluated after single or repeated administration (for 7 to 11 days) of TMC278 25, 75, or 150 mg once daily in non-HIV infected subjects.

In all drug-drug interaction trials, safety observations were comparable between the treatment phase in which subjects used the respective concomitant medications (together with TMC278) versus the treatment phase when they did not (TMC278 alone). Both by SOC and PT, no relevant differences in the incidence of AEs were observed between treatment phases.

In general, the exposure to TMC278 can be affected by modulators of cytochrome P450 (CYP) 3A enzyme activity and by drugs that increase the gastric pH.

The metabolism of TMC278 is mainly catalyzed by CYP3A enzymes. Therefore, co-administration of TMC278 and drugs that induce CYP3A could decrease TMC278 plasma concentrations, which could potentially reduce the therapeutic effect of TMC278. This decrease in exposure was indeed shown by the results of drug-drug interaction trials with rifampin and rifabutin, which both significantly decreased the exposure to TMC278. Based on this, TMC278 should not be used in combination with inducers of CYP3A.

Conversely, co-administration of TMC278 and drugs that inhibit CYP3A may increase TMC278 plasma concentrations, as evidenced by the results of drug-drug interaction trials with ketoconazole and ritonavir-boosted PIs. The increase in TMC278 exposure (based on Cmax) compared to the exposure obtained with TMC278 25 mg once daily that can still be assumed to have no discernable effect on the QTc interval (ie, upper limit of the 90% CI of the mean QTcF interval prolongation < 10 ms), was determined with simulations based on the pooled data of the TQT studies with TMC278 (25 to 300 mg once daily) in healthy volunteers. In none of the performed drug-drug interaction trials, including several with CYP3A inhibitors, did the Cmax of TMC278 increase by more than 85%. The observed interactions are thus not expected to be of clinical relevance or cause safety concerns, and therefore do not result in the need for dose adjustment.

The solubility of TMC278 is pH dependent (ie, reduced solubility at higher pH). Drugs that alter intragastric pH may affect the solubility of TMC278 and can therefore indirectly affect the absorption of TMC278. This was shown in drug-drug interaction trials with omeprazole and famotidine, which both significantly decreased the exposure to TMC278 when coadministered. Based on this, TMC278 should not be used in combination with proton pump inhibitors as

coadministration may cause significant decreases in TMC278 plasma concentrations. This may result in loss of therapeutic effect of TMC278. For drugs with a short-lived effect on intragastric pH, such as the H2-antagonists and antacids, an effect on TMC278 exposure can be circumvented by separating the intake of the drugs in time, as has been shown in a drug-drug interaction trial with famotidine. The combination of TMC278 and H2-receptor antagonists or antacids should be used with caution as coadministration may cause significant decreases in TMC278 plasma concentrations. H2-receptor antagonists should only be administered either 12 hours before or 4 hours after TMC278, and antacids should only be administered either 2 hours before or 4 hours after TMC278.

No additional data for pediatric subjects are available. No differences are expected in comparison with adults.

### 5.3.3. FTC

Based on the results of the in vitro experiments, in vivo assessments, and the known elimination pathways of FTC, the potential for clinically relevant drug interactions involving FTC with other medicinal products is low (m2.7.2, Section 3.2).

## 5.4. Use in Pregnancy and Lactation

No adequate and well-controlled studies of FTC/RPV/TAF, or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of FTC, RPV, or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. In animal studies, RPV had no effect on fertility and early embryonic and fetal development. Teratogenicity studies in rats and rabbits showed no teratogenic potential. The exposures at the embryo-fetal No Observed Adverse Effects Levels in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg taken once daily RPV. Studies in animals have shown limited placenta passage of RPV. It is not known whether placental transfer of RPV occurs in pregnant women. The FTC/RPV/TAF tablet should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In animal studies, it has been shown that TFV is excreted into milk. In humans, samples of breast milk obtained from 5 HIV-infected mothers given TVD show that TFV is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the TFV $IC_{50}$){17083}. The same samples show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC $IC_{50}$ but 3 to 12 times lower than the $C_{min}$ achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown. Tenofovir-associated risks, including the risk of viral resistance to TFV, in infants breastfed by mothers being treated with TAF are unknown. It is not known whether RPV is excreted in human milk. No data on lactation are available from trials. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving the FTC/RPV/TAF FDC.

### 5.4.1. E/C/F/TAF

No pregnancies were reported in Phase 1 studies with the E/C/F/TAF FDC.

Two pregnancies were reported in the Phase 2 Study GS-US-292-0102. One subject (Subject [redacted], E/C/F/TAF) had a confirmed ectopic pregnancy on Day 689 that was reported as an SAE. The subject underwent emergency surgery to remove the ectopic pregnancy and she recovered on Day 690. One subject (Subject [redacted], STB) had a confirmed pregnancy on Day 741 for which further details were not available.

Six pregnancies were reported in Phase 3 Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0112, and GS-US-292-0109; all were due to nonadherence to protocol-specified contraception.

Pregnancy in 1 subject enrolled in Study GS-US-292-0104 (Subject [redacted], STB) resulted in the birth at 40 weeks gestation of a live-born female neonate; there were no reported complications.

Pregnancy in 1 subject enrolled in Study GS-US-292-0111 (Subject [redacted], STB) reported severe intrauterine growth restriction. The subject delivered a live male infant at 37 weeks gestational age; no labor or delivery complications, nor prolonged neonatal hospitalization were noted.

Pregnancies in 3 subjects enrolled in Study GS-US-292-0111 (Subjects [redacted], [redacted], and [redacted]; STB) were reported as ongoing at the time of the report.

Pregnancy in 1 subject enrolled in Study GS-US-292-0109 (Subject [redacted], E/C/F/TAF) was terminated by an elective abortion.

No pregnancies were reported in Study GS-US-292-0112 or GS-US-292-0106.

### 5.4.2. RPV

In the two Phase 3 trials, 3 pregnancies were reported during treatment with RPV after drug exposure ranging from 59 days to approximately 10 months. All 3 subjects subsequently discontinued the trial. One subject gave birth prematurely by Caesarean section as there were no contractions. The baby was born healthy, with no reported anomalies. Another subject gave birth to a healthy baby girl. Details of the other birth are unavailable at this time. No additional pregnancies were reported in the RPV group in the Phase 3 Week 96 pooled analysis.

In the Phase 2b trial, 3 pregnancies were reported during treatment with RPV after drug exposure ranging from 394 to 673 days. All 3 subjects subsequently discontinued the trial. One of the 3 subjects experienced pre-eclampsia and gave birth prematurely by Caesarean section, but all 3 pregnancies resulted in healthy live births. No additional pregnancies were reported in the RPV group in the Week 240 analysis.

Pregnancy and breastfeeding were exclusion criteria in C213, hence no additional data are available.

### 5.4.3. Complera/Eviplera

No pregnancies were reported during Studies GS-US-264-0111 and GS-US-264-0106.

### 5.4.4. FTC/RPV/TAF

No pregnancies were reported in the Phase 1 studies with FTC/RPV/TAF.

### 5.4.5. F/TAF

No pregnancies were reported in the Phase 1 studies with F/TAF included in this submission.

### 5.4.6. TAF

No pregnancies were reported in clinical studies for TAF single agent included in this submission.

### 5.4.7. FTC

Pregnancies in clinical studies are described in individual CSRs. The safety of the use of FTC during pregnancy or breast-feeding is reflected in the approved drug label for Emtriva. This product should only be used in pregnancy if the potential benefit justifies the potential risk.

### 5.4.8. Antiretroviral Pregnancy Registry

Cumulative Antiretroviral Pregnancy Registry interim analysis reports are produced at 6-month intervals, and the latest report was issued in December 2014 (data to 31 July 2014). The cumulative data for FTC are provided below.

A total of 1721 first trimester exposure and 818 second/third trimester exposure prospective cases of live births involving exposure to FTC were presented. There were 41 cases of birth defects following first trimester exposure and 18 cases of a birth defects following second/third trimester exposure. The prevalence of defects per 100 live births for first trimester exposures to FTC is 2.4% (95% CI: 1.7% to 3.2%) and 2.2% (95% CI: 1.3% to 3.5%) with earliest exposure to FTC in the second/third trimester.

A total of 81 first trimester exposure and 58 second/third trimester exposure prospective cases of live births involving exposure to RPV were presented. No birth defects were reported following first trimester exposure and one case of birth defect was reported during the second/third trimester exposure.

A total of 2330 first trimester exposure and 1112 second/third trimester exposure prospective cases of live births involving exposure to TDF were presented. There were 53 cases of birth defects following first trimester exposure and 24 cases of birth defects following second/third trimester exposure. The prevalence of defects per 100 live births for first trimester exposures to

TDF is 2.3% (95% CI: 1.7% to 3.0%) and 2.2% (95% CI: 1.4% to 3.2%) with earliest exposure to tenofovir DF in the second/third trimester.

For FTC and TDF, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. For RPV, there are insufficient data to make similar comparison with other drugs or specific subgroups of defects.

## 5.5. Overdose

If an overdose with FTC/RPV/TAF occurs, the patient must be monitored for evidence of toxicity, and general supportive measures applied as necessary, including observation of the clinical status of the patient and monitoring of vital signs. Electrocardiogram monitoring is recommended due to the possibility of QT interval prolongation associated with RPV.

Limited clinical experience is available at doses higher than the therapeutic doses of FTC, RPV, or TAF. Supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see Section 2.1.9.5.2). No Grade 3 adverse reactions were reported at supratherapeutic doses in studies of FTC. In RPV trial C131, subjects received a supratherapeutic dose of RPV (300 mg taken once daily daily) for 11 days, which was generally well tolerated (mean $C_{max}$ = 1665 ± 398.1 ng/mL). In trial C112, subjects received RPV 150 mg taken once daily with Darunavir/RTV 800/100 mg for 11 days (mean $C_{max}$ = 1860 ± 673 ng/mL), which was also generally well tolerated. In comparison, the mean $C_{max}$ value as observed in HIV-infected subjects at a 25 mg taken once daily dose was 134 ± 72 ng/mL (m2.7.2, Section 3.3.1.1.2).

Up to 30% of the FTC dose may be removed by hemodialysis. TFV is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether FTC or TFV may be removed by peritoneal dialysis. Since RPV is highly protein bound, dialysis is unlikely to result in significant removal of the active substance. If indicated, elimination of unabsorbed RPV is to be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed RPV.

Within the Phase 1, 2 and 3 studies included in this submission, most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of study medication and not associated with clinical symptoms or sequelae. Cases with additional relevant details are described below:

- In E/C/F/TAF Study GS-US-292-0104, 2 subjects had AEs associated with overdose: (E/C/F/TAF: Grade 1 headache [Subject [redacted]], and event not specified [Subject [redacted]]).

- In E/C/F/TAF Study GS-US-292-0111, 2 subjects had AEs associated with overdose (E/C/F/TAF: dizziness [Subject [redacted]], STB: vomiting [Subject [redacted]]).

- In E/C/F/TAF Study GS-US-292-0102, Subject [redacted] in the STB group had an SAE of suicidal ideation by taking 3 pills from each bottle of the study drugs instead of the prescribed dose of 1 dose form daily. The subject also took an overdose of naproxen by taking more than 6 pills at the same time on the same day. The SAE of suicidal ideation resolved on the day of onset.

- In E/C/F/TAF Study GS-US-292-0109, Subject [redacted] in the E/C/F/TAF group took almost an entire bottle of study drug in a suicidal gesture (intentional overdose). The suicide attempt was reported as an SAE that resolved on the same day as onset. Study drug was discontinued, and the subject recovered fully.

## 5.6. Drug Abuse

No safety issues concerning the abuse or misuse of FTC/RPV/TAF tablets are anticipated from the available data.

## 5.7. Withdrawal and Rebound

The safety and efficacy of FTC/RPV/TAF have not been established in patients coinfected with HIV-1 and HBV. Discontinuation of FTC/RPV/TAF therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis. Patients coinfected with HIV-1 and HBV who discontinue FTC/RPV/TAF should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since posttreatment exacerbation of hepatitis may lead to hepatic decompensation.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of FTC, RPV, or TAF on the ability to drive or operate machinery.

# 6. POSTMARKETING DATA

As FTC/RPV/TAF has not been approved, no postmarketing data are available. Relevant postmarketing data for Complera/Eviplera are presented below.

Cumulative patient exposure to Complera/Eviplera since first marketing approval in the US on 10 August 2011 to 28 February 2015 is estimated to be 206,654 patient years. Since first marketing approval of Complera/Eviplera, postmarketing data is regularly reviewed in periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs) that are submitted to regulatory authorities worldwide. Up until the data cut date of the last Complera/Eviplera PSUR/PBRER on 10 February 2015, no postmarketing ADRs had been identified for Complera/Eviplera or its rilpivirine component; the safety profiles of the emtricitabine and tenofovir DF components of Complera/Eviplera were well established at the time of first marketing approval and similarly no new postmarketing ADRs have been identified for these components.

Since the data cut date of the last Complera/Eviplera PSUR/PBRER on 10 February 2015, 2 postmarketing ADRs for Complera/Eviplera have been identified and text describing these ADRs has been added to the Complera/Eviplera CCDS:

- Severe skin and hypersensitivity reactions
- Weight gain

Neither of these ADRs could be attributed to an individual component of Complera/Eviplera, given that they were identified in patients receiving the Complera/Eviplera FDC. They have, therefore, been described as ADRs to Complera/Eviplera in the CCDS and are also considered relevant for FTC/RPV/TAF.

## 6.1. Severe Skin and Hypersensitivity Reactions

A cumulative review of severe skin and hypersensitivity reactions with Complera/Eviplera was prompted by receipt of a FDA Safety Labeling Change Notification for Complera to update the Complera US Prescribing Information with Warnings and Precautions describing severe skin and hypersensitivity reactions (m5.3.6, Complera/Eviplera Severe Skin and Hypersensitivity Reactions Cumulative Safety Review). The aim of the cumulative review was to determine whether there was a causal association between severe skin and hypersensitivity reactions and Complera/Eviplera, and whether an update to the Complera/Eviplera CCDS was warranted. The following sources of information were assessed in the cumulative review: cases on the Gilead Drug Safety and Public Health (DSPH) database, information from clinical trials, information from epidemiology studies, information from disproportionality analysis, information from the published literature and information from nonclinical sources.

Upon comprehensive review of all available data, the following conclusions were made:

- There have been reports of possible angioedema in patients receiving Complera/Eviplera, and these reports are consistent in terms of nature and severity with current labeling, where angioedema is considered an ADR to the tenofovir DF component of Complera/Eviplera. However, it is not possible to attribute angioedema to a particular component of Complera/Eviplera from the cases received.

- Cases of serious or severe skin or allergic reactions with systemic symptoms, including fever, blisters, conjunctivitis, elevated liver function tests and eosinophilia have been reported for Complera/Eviplera. Additional wording in Complera/Eviplera labeling to indicate that severe skin reactions with systemic symptoms have been reported was considered warranted.

The Undesirable Effects section of the Complera/Eviplera CCDS was updated to Version 7 (08 April 2015) to include the following postmarketing experience text for Complera/Eviplera:

"*SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Severe skin reactions with systemic symptoms have been reported during postmarketing experience, including rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia*."

## 6.2. Weight Increase

A cumulative review of weight gain with Complera/Eviplera was undertaken following receipt of a literature article describing weight gain in 4 HIV-1 infected patients switching to Complera/Eviplera {32612}, in the context of a growing number of postmarketing cases of weight gain for Complera/Eviplera on the Gilead DSPH database (m5.3.6, Complera/Eviplera Weight Gain Cumulative Safety Review). At the time of writing the cumulative review, no events relevant to weight gain were described in the Complera/Eviplera CCDS. In the cumulative review, an analysis of weight gain was performed using the following sources of data: cases on the Gilead DSPH database, disproportionality analysis, information from clinical trials, information from epidemiological studies, information from the published literature, and information from nonclinical studies.

Following review of all data, in particular the postmarketing data, with supporting data from clinical trials, it was concluded that there was sufficient evidence to add weight gain to the Complera/Eviplera CCDS as an ADR for Complera/Eviplera identified through postmarketing experience.

Therefore, the Complera/Eviplera CCDS was updated to Version 8 (04 May 2015) to include the following postmarketing ADR for Complera/Eviplera:

"*METABOLISM AND NUTRITION DISORDERS: Weight increased.*"

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# 8. APPENDIX

| Appendix Number | Appendix Title |
|---|---|
| 8.1 | Tabular Summaries of Studies Relevant for Safety |
| 8.2 | E/C/F/TAF FDC: Integrated Safety Analyses |

## 8.1. Tabular Summaries of Studies Relevant for Safety

### 8.1.1. E/C/F/TAF Studies

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | GS-US-292-0106 (synopsis) | Part A: Evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC<br>Part B: Evaluate the safety and tolerability of the E/C/F/TAF FDC | Phase 2/3, open-label, multicenter, 2-part, single-group study | E/C/F/TAF (150/150/200/10 mg) QD PO | 48 weeks<br>Extension Phase: Subjects have option to continue study drug until subject turns 18 and E/C/F/TAF is commercially available for adults in country of enrollment, E/C/F/TAF becomes commercially available for adolescents in country of enrollment, or E/C/F/TAF development is terminated in country of enrollment | Enrolled: 48<br>Part A: 24<br>Part B: 24<br>Safety Analysis Set: 48<br>Continuing study drug at Week 24:<br>Main study: 47<br>Extension: 1 | HIV infected, ART-naive adolescents (12 to < 18 years of age) | Study ongoing; Week 24 Interim CSR |
| Uncontrolled Clinical Studies | GS-US-292-0112 (synopsis) | Evaluate the effect of the E/C/F/TAF FDC on renal parameters | Phase 3, open-label, multicenter, multi-cohort study | E/C/F/TAF (150/150/200/10 mg) QD PO | 96 weeks<br>Extension Phase: Subjects have option to continue study drug until E/C/F/TAF is commercially available or development is terminated | Enrolled: 252<br>Safety Analysis Set:<br>Cohort 1: 242<br>Cohort 2: 6<br>Continuing study drug at Week 24<br>Cohort 1: 226<br>Cohort 2: 6 | HIV-infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min<br>Cohort 1: ART-experienced<br>Cohort 2: ART-naive | Study ongoing;<br>Week 24 Interim CSR |

## 8.1.2. RPV Studies

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | TMC278-TiDP38-C213 (C213; PAINT) (synopsis) | Determine the effect of steady-state (multiple dose) PK and short-term safety and efficacy of TMC278 in adolescents | Phase 2, open-label, single arm study | Once daily dose of TMC278 25 mg, under fed conditions, plus 2 investigator selected N(t)RTIs: AZT,ABC, or TDF in combination with 3TC or FTC (AZT/3TC, AZT/FTC, ABC/3TC, ABC/FTC, TDF/FTC, or TDF/3TC) | 48 Weeks | Randomized and Treated: 36<br>Completed: 4<br>Ongoing: 24 | HIV-1 infected treatment naïve adolescents (12 to < 18 years) | Study ongoing,<br>Week 48 Interim CSR[a] |

a. Study is on file with dossier submitted by Tibotec/Janssen

## 8.1.3. TAF Studies

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Patient PD and PK/PD | GS - 120-1101 (synopsis) | Investigate the safety of TAF over 14 days, and evaluate the antiviral potency of escalating doses of TAF compared with TDF in ARTnaive HIV infected subjects | Phase 1/2, randomized, double-blind, active controlled, dose-escalation study | Within each cohort, subjects were randomized to 1 of the following treatments:<br>Cohort 1:<br>• TAF 50 mg (2 × 25-mg tablets) + placebo-to-match TDF QD PO (A)<br>• Placebo-to-match TAF + TDF 300-mg tablet QD PO (B)<br>Cohort 2:<br>• TAF 150 mg (6 × 25-mg tablets) + placebo-to-match TDF QD PO (C)<br>• Placebo-to-match TAF + TDF 300-mg tablet QD PO (D) | 14 days | Randomized: 30<br>Completed: 30<br>Safety Analysis Set:<br>A: 10<br>B + D: 10<br>C: 10 | HIV infected, ART-naive adult subjects | Study completed; Final CSR |

## 8.1.4. FTC Studies

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | FTC-301A (synopsis) | Compare the safety and efficacy of FTC and d4T within a triple drug combination containing ddI and EFV | Phase 3, randomized (1:1), double-blind, active-controlled equivalence study | FTC 200 mg QD PO (A)<br>d4T 40 mg BID PO if ≥ 60 kg; 30 mg BID PO if < 60 kg (B)<br>Both groups: ddI 400 mg QD PO if ≥ 60 kg; 250 mg QD PO if < 60 kg and EFV 600 mg QD PO | 48 weeks: Last subject completed 48 weeks on 24 Oct 2002; all subjects subsequently rolled to an open-label FTC-containing regimen or an alternative regimen off study | Randomized and received ≥ 1 dose of study drug (ITT): 571<br>A: 286<br>B: 285 | HIV infected, ART-naive subjects | Study completed;<br>Interim Week 48 CSR (Volume 1 and Volume 2) |
| Controlled Clinical Studies Pertinent to the Claimed Indication | FTC-302 (synopsis) | Compare the safety and efficacy of FTC to 3TC when used in combination d4T and either NVP orEFV | Phase 3, randomized (1:1), partially blinded, open-label, active-controlled study | Subjects were stratified per HIV-1 RNA levels, then randomized (1:1) to either FTC or 3TC (placebo blinded) plus open-label background therapy consisting of d4T[a] plus either NVP[b] or EFV and received:<br>FTC 200 mg QD PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 194) or EFV 600 mg QD PO (n = 40) (A)<br>3TC 150 mg BID PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg BID and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 191) or EFV 600 mg once daily PO (n = 43) (B) | 48 weeks | Randomized: 512<br>ITT: 468<br>A: 234<br>B: 234 | HIV infected, ART-naive adult subjects | Study completed;<br>Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | FTC-303 (synopsis) | Compare FTC to 3TC in HIV infected subjects with HIV-1 RNA ≤ 400 copies/mL on a stable (≥ 12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI | Phase 3, randomized (2:1) open-label, multi-center equivalence study | Subjects switch from 3TC to FTC PO while continuing on current background therapy (A)<br>Subjects continue on current 3TC-containing regimen (B) | 48 weeks | Randomized: 459<br>ITT: 440<br>A: 294<br>B: 146 | HIV infected, 3TC-experienced, adult subjects with stable HIV-1 RNA | Study completed;<br>Final CSR and Addendum |
| Uncontrolled Clinical Studies | FTC 203 (synopsis) | Obtain long-term safety, PK, and antiviral activity of FTC in pediatric subjects | Phase 2, multicenter, open-label study in ART-naive and ART-experienced male or female pediatric patients.<br>ART-naive patients had no or very limited prior ART exposure. | ART-naive (triple-drug ART regimen):<br>FTC (6 mg/kg QD; up to 200 mg capsule or 240 mg oral solution QD)<br>d4T (mg/kg BID dosage based on weight):<br>1 mg/kg (< 30 kg); 30 mg/kg (30–59 kg); 40 mg/kg (≥ 60 kg)<br>LPV/r (mg/kg BID dosage based on weight):<br>12/3 mg/kg (7-< 15 kg);<br>10/2.5 mg/kg (15-40 kg);<br>400/100 mg/kg (> 40 kg)<br>ART-experienced:<br>FTC (same dosage as above) plus background ART medications (no 3TC)<br>No control regimen | 96 weeks | Enrolled: 117<br>ITT: 116<br>ART-naive: 71<br>ART-experienced: 45<br>Age groups:<br>3–24 mo: 16<br>25 mo–6 y: 68<br>7–12 y: 29<br>13–17 y: 3 | Pediatric subjects (3 mo-17 y) with HIV infection, CD4+ > 200 cells/mm3;<br>ART-naive: Plasma HIV-1 RNA 5,000-600,000 copies/mL<br>ART-experienced: HIV-1 RNA ≤ 400 copies/mL, stable on 3TC regimen for ≥ 3 mo | Study completed;<br>Final Week 48 CSR |

a Subjects were allowed to switch from d4T to AZT if toxicity occurred
b Subject were allowed to switched from NVP to EFV if toxicity occurred

## 8.2. E/C/F/TAF FDC: Integrated Safety Analyses

Table 1 Subject Disposition, Studies GS-US-292-0104 and GS-US-292-0111, All Randomized Subjects

Table 2 Demographics and Baseline Characteristics, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 3 Baseline Disease Characteristics, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 4 Duration of Exposure to Study Drug, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 5 Time to Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 5.1 Supporting Table for Table 5: Percentiles of Time to Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 5.2 Supporting Table for Table 5: Listing of Time and Censoring Status of Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 6 Treatment-Emergent Adverse Events: Overall Summary, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 7 Treatment-Emergent Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 8.1 Treatment-Emergent Adverse Events by Age Group (< 50 Years or ≥ 50 Years), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 8.2 Treatment-Emergent Adverse Events by Sex (Male or Female), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 8.3 Treatment-Emergent Adverse Events by Race (Black or Nonblack), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

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SECTION 2.7.4 — SUMMARY OF CLINICAL SAFETY

# EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (FTC/RPV/TAF FDC)

## LEGACY APPENDICES

**Gilead Sciences**

18 June 2015

CONFIDENTIAL AND PROPRIETARY INFORMATION

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# 1. SAFETY OF FTC

The principal sources of safety data for FTC that contribute to this summary of clinical safety are the pooled analysis of 48-week data from the Phase 3 Studies FTC-301A, FTC-302, and FTC-303 in a total of 1479 HIV-1 infected adult subjects either ART-naive (Studies FTC-301A and FTC-302) or on stable ART (Study FTC-303), as well as data from Study FTC-203, a Phase 2, open-label study of FTC in combination with other antiretroviral agents in 116 HIV-1 infected pediatric subjects who were either ART-naive or -experienced. Key safety data from the integrated analysis are summarized in Section 1.1. Summaries of the methods and results for Studies FTC-301A, FTC-302, FTC-303, and FTC-203 are provided in Sections 1.2 to 1.5, respectively.

## 1.1. Summary of Integrated Safety Data for FTC

### 1.1.1. Treatment Groups

Treatment group data from the 3 principal adult safety studies for FTC are summarized in Table 1.

**Table 1. Emtricitabine: Summary of Treatment Groups and Exposure in Principal Safety Studies**

| Study | Duration | Treatment Group | Number of Subjects |
|---|---|---|---|
| FTC-301A | 48 weeks | Arm 1: FTC 200 mg once daily plus ddI (400 mg once daily if ≥ 60 kg; 250 mg once daily if < 60 kg) + EFV (600 mg once daily)<br>Arm 2: d4T 40 mg BID if ≥ 60 kg or 30 mg BID if < 60 kg plus ddI 400 mg once daily if ≥ 60 kg or 250 mg once daily if < 60 kg, plus EFV 600 mg once daily | N = 571<br>Arm 1: n = 286<br>Arm 2: n = 285 |
| FTC-302 | 48 weeks | Arm 1: FTC 200 mg once daily plus d4T 30 mg BID if < 60 kg or 40 mg BID if ≥ 60 kg and NVP 200 mg once daily for 14 days then 200 mg BID (n = 194) or EFV 600 mg once daily (n = 40)<br>Arm 2: 3TC 150 mg BID plus d4T 30 mg BID if < 60 kg or 40 mg BID if ≥ 60 kg BID and NVP 200 mg once daily for 14 days then 200 mg BID (n = 191) or EFV 600 mg once daily (n = 43) | N = 468<br>Arm 1: n = 234<br>Arm 2: n = 234 |
| FTC-303 | 48 weeks | Arm 1: subjects switch from 3TC to FTC while continuing on current background therapy<br>Arm 2: subjects continuing on current 3TC-containing regimen | N = 440<br>Arm 1: n = 294<br>Arm 2: n = 146 |

### 1.1.2. Demographic and Other Characteristics of the Study Population

Demographics and baseline characteristics were assessed for the pooled safety population of adult subjects from Studies FTC-301A, FTC-302, and FTC-303 and are presented in Table 2. In each of the 3 controlled studies, treatment groups were similar with regard to demographic and baseline characteristics. Of the 814 FTC-treated subjects in the 3 studies, the majority (72%) was male, and most were either African (36%) or Caucasian (43%). Mean age was 37.2 years, with a range of 18 to 70 years. The demographic characteristics of the FTC-treated population in these studies are representative of an HIV-1 infected population, and allow generalized conclusions regarding safety across demographic groups. The mean plasma HIV-1 RNA value was 3.6 $\log_{10}$ c/mL (for entry into Study FTC-303, ≤ 400 c/mL was required), and the mean CD4+ cell count was 412 cells/$mm^3$.

**Table 2. FTC-301A, FTC-302, and FTC-303: Demographics and Baseline Disease Characteristics in HIV-1 Infected Adults**

| | FTC-301A | | FTC-302 | | FTC-303 | | |
|---|---|---|---|---|---|---|---|
| | FTC | d4T | FTC | 3TC | FTC | 3TC | Total FTC |
| No. of Subjects | 286 | 285 | 234 | 234 | 294 | 146 | 814 |
| Age (years) | | | | | | | |
| Mean | 35.8 | 36.5 | 33.1 | 32.1 | 41.7 | 42.6 | 37.2 |
| Min–Max | 18-67 | 18-69 | 18-59 | 18-63 | 22–70 | 23–80 | 18-70 |
| Sex (n, %) | | | | | | | |
| Male | 239 (84) | 246 (86) | 99 (42) | 94 (40) | 250 (85) | 127 (87) | 588 (72) |
| Female | 47 (16) | 39 (14) | 135 (58) | 140 (60) | 44 (15) | 19 (13) | 226 (28) |
| Race (n, %) | | | | | | | |
| Caucasian | 136 (48) | 159 (56) | 24 (10) | 34 (15) | 193 (66) | 87 (60) | 353 (43) |
| African | 52 (18) | 40 (14) | 186 (80) | 174 (74) | 59 (20) | 34 (23) | 297 (36) |
| Hispanic | 77 (27) | 70 (25) | 0 (0) | 0 (0) | 34 (12) | 24 (16) | 111 (14) |
| Other | 21 (7) | 16 (5) | 24 (10) | 26 (11) | 8 (3) | 1 (1) | 53 (7) |
| Plasma HIV-1 RNA ($\log_{10}$ c/mL) | | | | | | | |
| Mean | 4.8 | 4.8 | 4.5 | 4.5 | 1.8 | 1.8 | 3.6 |
| Min–Max | 2.6-7.0 | 2.6-6.5 | 2.4-5.9 | 2.6-5.9 | 1.7–3.6 | 1.7–4.0 | 1.7-7.0 |
| CD4+ Cell Count (cells/$mm^3$) | | | | | | | |
| Mean | 312 | 324 | 392 | 386 | 525 | 533 | 412 |
| Min–Max | 5-1156 | 6-1317 | 106-1348 | 129-1419 | 37–1478 | 61–1909 | 5-1478 |

### 1.1.3. Adverse Events

Table 3 displays the most common clinical AEs (occurring in ≥ 3% of subjects treated with FTC) reported during 48 weeks of treatment in Studies FTC-301A, FTC-302, and FTC-303.

Overall, 94% of FTC-treated subjects and 97% of subjects in the combined control group experienced ≥ 1 treatment-emergent AE during these long-term, controlled studies in HIV-1 infected adults. The AE profile observed for FTC was comparable to that observed for the combined comparator group. The most common treatment-emergent AEs among FTC-treated subjects were infection (33% FTC group; 43% control group), diarrhea (22% FTC group; 27% control group), headache (22% FTC group; 25% control group), nausea (17% FTC group; 19% control group), rash (17% FTC group; 18% control group), flu syndrome (15% FTC group; 16% control group), pain (15% FTC group; 15% control group), and asthenia (14% FTC; 14% control group).

Adverse events for each study are further described in the narratives in Sections 1.2 to 1.4.

**Table 3. FTC-301A, FTC-302, and FTC-303 (0–48 Weeks): Pooled Adverse Events by Body System Reported in ≥ 3% Emtricitabine-Treated Subjects**

| | Week 48 Pooled Safety Population (Controlled Studies) | | | |
|---|---|---|---|---|
| | FTC (N = 814) | | Control (N = 665) | |
| | n | % | n | % |
| Total reporting ≥ 1 event | 761 | 93.5% | 642 | 96.5% |
| Body as a Whole | 596 | 73.2% | 511 | 76.8% |
| Abdominal Pain | 105 | 12.9% | 107 | 16.1% |
| Asthenia | 113 | 13.9% | 93 | 14.0% |
| Accidental injury | 76 | 9.3% | 72 | 10.8% |
| Back pain | 69 | 8.5% | 67 | 10.1% |
| Chest pain | 29 | 3.6% | 29 | 4.4% |
| Fever | 44 | 5.4% | 38 | 5.7% |
| Flu syndrome | 123 | 15.1% | 105 | 15.8% |
| Headache | 178 | 21.9% | 163 | 24.5% |
| Infection | 269 | 33.0% | 227 | 43.1% |
| Pain | 119 | 14.6% | 102 | 15.3% |
| Cardiovascular System | 77 | 9.5% | 76 | 11.4% |
| Hypertension | 25 | 3.1% | 19 | 2.9% |

| | Week 48 Pooled Safety Population (Controlled Studies) | | | |
|---|---|---|---|---|
| | FTC (N = 814) | | Control (N = 665) | |
| | n | % | n | % |
| Digestive System | 432 | 53.1% | 406 | 61.1% |
| Anorexia | 35 | 4.3% | 32 | 4.8% |
| Constipation | 32 | 3.9% | 27 | 4.1% |
| Diarrhoea | 179 | 22.0% | 176 | 26.5% |
| Dyspepsia | 46 | 5.7% | 50 | 7.5% |
| Flatulence | 25 | 3.1% | 25 | 3.8% |
| Gastroenteritis | 36 | 4.4% | 49 | 7.4% |
| Nausea | 141 | 17.3% | 128 | 19.2% |
| Oral moniliasis | 25 | 3.1% | 21 | 3.2% |
| Rectal disorder | 26 | 3.2% | 27 | 4.1% |
| Vomiting | 91 | 11.2% | 80 | 12.0% |
| Hemic and Lymphatic System | 115 | 14.1% | 89 | 13.4% |
| Leukopenia | 31 | 3.8% | 19 | 2.9% |
| Lymphadenopathy | 65 | 8.0% | 49 | 7.4% |
| Metabolic and Nutritional System | 214 | 26.3% | 213 | 32.0% |
| Amylase increased | 26 | 3.2% | 39 | 5.9% |
| Creatine phosphokinase increased | 25 | 3.1% | 32 | 4.8% |
| Hyperlipaemia | 31 | 3.8% | 29 | 4.4% |
| SGOT increased | 24 | 2.9% | 61 | 9.2% |
| SGPT increased | 64 | 7.9% | 74 | 11.1% |
| Musculoskeletal System | 120 | 14.7% | 97 | 14.6% |
| Arthralgia | 34 | 4.2% | 33 | 5.0% |
| Myalgia | 42 | 5.2% | 22 | 3.3% |
| Nervous System | 345 | 42.4% | 343 | 51.6% |
| Abnormal dreams | 38 | 4.7% | 57 | 8.6% |
| Anxiety | 57 | 7.0% | 43 | 6.5% |
| Depression | 51 | 6.3% | 67 | 10.1% |
| Dizziness | 100 | 12.3% | 109 | 16.4% |
| Insomnia | 75 | 9.2% | 77 | 11.6% |
| Peripheral neuritis/neuropathy | 37 | 4.5% | 55 | 8.3% |
| Somnolence | 37 | 4.5% | 36 | 5.4% |

| | Week 48 Pooled Safety Population (Controlled Studies) | | | |
|---|---|---|---|---|
| | FTC (N = 814) | | Control (N = 665) | |
| | n | % | n | % |
| Respiratory System | 348 | 42.8% | 282 | 42.4% |
| Bronchitis | 68 | 8.4% | 78 | 11.7% |
| Cough increased | 107 | 13.1% | 67 | 10.1% |
| Pharyngitis | 107 | 13.1% | 89 | 13.4% |
| Pneumonia | 21 | 2.6% | 14 | 2.1% |
| Rhinitis | 106 | 13.0% | 67 | 10.1% |
| Sinusitis | 42 | 5.2% | 45 | 6.8% |
| Skin and Appendages | 381 | 46.8% | 316 | 47.5% |
| Acne | 27 | 3.3% | 25 | 3.8% |
| Fungal dermatitis | 82 | 10.1% | 69 | 10.4% |
| Herpes simplex | 61 | 7.5% | 43 | 6.5% |
| Pruritus | 51 | 6.3% | 38 | 5.7% |
| Rash | 138 | 17.0% | 118 | 17.7% |
| Skin benign neoplasm | 32 | 3.9% | 30 | 4.5% |
| Skin discolouration | 27 | 3.3% | 5 | 0.8% |
| Special Senses | 109 | 13.4% | 80 | 12.0% |
| Conjunctivitis | 33 | 4.1% | 33 | 5.0% |
| Fungal dermatitis | 82 | 10.1% | 69 | 10.4% |
| Urogenital System | 174 | 21.4% | 152 | 22.9% |
| Leukorrhoea[a] | 9 | 4.0% | 13 | 6.6% |
| Metrorrhagia[a] | 7 | 3.1% | 2 | 1.0% |
| Salpingitis[a] | 13 | 5.8% | 12 | 6.1% |
| Urinary tract infection | 27 | 3.3% | 23 | 3.5% |
| Vaginal moniliasis[a] | 21 | 9.3% | 16 | 8.1% |
| Vaginitis[a] | 12 | 5.3% | 12 | 6.1% |

a Based on the number of female subjects in the ITT population.

### 1.1.4. Clinical Laboratory Evaluations

Overall, 30% of FTC-treated subjects and 32% of subjects in the combined control group experienced ≥ 1 laboratory abnormality ≥ Grade 3 in severity in pooled studies FTC-301A, FTC-302, and FTC-303. The most common Grade 3 or 4 laboratory abnormalities in FTC-treated subjects were increases in creatinine kinase, triglycerides, AST, and ALT. In each long-term study, the overall incidence of Grade 3 or 4 laboratory abnormalities was similar in the FTC-treated subjects and controls.

## 1.2. Study FTC-301A

### Title

A Randomized, Double-Blind, Equivalence Trial Comparing Emtricitabine to Stavudine within a Triple Drug Combination Containing Didanosine Plus Efavirenz in Antiretroviral-Drug Naive HlV-1 Infected Patients

### Objective

The primary objective of this study was to assess the safety and efficacy of FTC as compared to d4T when used within a BR containing another NRTI (ddI) and a NNRTI (EFV).

### Study Design/Subject Population

FTC-301A was a Phase 3, randomized, double-blind, double-dummy, multicenter study designed to evaluate the equivalence of FTC to d4T in HIV-1 infected subjects. At least 500 ART-naive subjects were to be randomized in a 1:1 ratio to 1 of the 2 treatment arms: FTC 200 mg once daily PO (Arm 1) or d4T 40 mg BID PO if ≥ 60 kg or 30 mg BID PO if < 60 kg (Arm 2). Subjects in both arms received EFV 600 mg once daily PO and ddI 400 mg once daily PO if ≥ 60 kg or 250 mg once daily PO if < 60 kg.

A total of 571 subjects (ITT population) were randomized and received ≥ 1 dose of study medication, 285 to d4T and 286 to FTC.

Further details on the design and results of this study are available in the FTC-301A Interim Week 48 CSR (Volume 1 and Volume 2).

### Efficacy Results

At Weeks 24 and 48, the proportion of subjects with plasma HIV-1 RNA ≤ 50 c/mL (primary endpoint, ITT population) was significantly higher in the FTC arm compared with the d4T arm. In the noncompleter = failure analysis at Week 24 using the ITT population, 80.9% of the FTC arm had suppression of plasma HIV-1 RNA ≤ 50 c/mL as compared to 69.6% of the d4T arm; the stratum-adjusted difference between treatment arms (d4T minus FTC) was −11.3%, which yielded a stratum-adjusted 95% CI of −18.0% to −4.6%. In the corresponding analysis at Week 48, 74.2% of subjects in the FTC arm had suppression of plasma HIV-1 RNA ≤ 50 c/mL as compared to 58.0% of the d4T arm (stratum-adjusted treatment −16.6%; 95% CI: −24.1% to −9.2%).

For all secondary endpoints at Weeks 24 and 48 (ITT population), the difference between FTC and d4T was statistically significantly different in favor of FTC. In particular, a statistically significant greater proportion of subjects in the FTC treatment arm (86.9%) had suppression of plasma HIV-1 RNA ≤ 400 c/mL as compared to the d4T treatment arm (79.3%) at Week 24; stratum-adjusted difference of −6.8% (95% CI of −12.6% to −1.0%). At Week 48, the corresponding response rates were 80.2% in the FTC arm as compared to 67.0% of the d4T arm (stratum-adjusted difference −12.9%; 95% CI: −19.7% to −6.0%).

**Virology Results**

Of the 541 virologic evaluable subjects, 58 were confirmed virologic failures at the time of the Week 48 data cutoff after a median duration of follow-up of 60 weeks, 41 (14.9%) subjects in the d4T treatment arm and 17 (6.4%) in the FTC treatment arm. Genotypic data were obtained for 57/58 subjects (16/17 failures in the FTC arm and 41/41 failures in the d4T arm) at baseline and at time of virologic failure. Genotypic analysis of isolates at the time of virologic failure showed that 11/16 subjects in the FTC arm and 35/41 subjects in the d4T arm developed new mutations associated with study drug. With or without adjusting for baseline mutations, analysis confirmed a statistically lower incidence of virologic failure in FTC-treated subjects.

**Safety Results**

Permanent discontinuation of study regimen at Week 24 due to clinical AEs (tolerability failure) occurred in 5.3% of subjects in the d4T treatment arm and in 3.8% of subjects in the FTC treatment arm. For the ITT population through Week 48, a statistically significant greater proportion of subjects in the d4T treatment arm were considered tolerability failures as compared to the FTC treatment arm. The stratum-adjusted difference between treatment arms was 5.3%, which yielded a stratum-adjusted 95% CI of 0.8% to 9.8%. The estimate of the KM probability of tolerability failure was consistent with the observed proportion of tolerability failures.

The overall incidence of AEs was similar in both treatment arms during the 48-week study period (98% and 96% of subjects in the d4T and FTC arms, respectively, experienced at ≥ 1 AE). The incidence of most AEs was comparable between treatment arms with some exceptions where statistically significant differences were observed: diarrhea (34.0% d4T; 24.1% FTC), nausea (23.5% d4T; 13.6% FTC), paresthesia (12.3% d4T; 5.9% FTC), neuropathy (13.0% d4T; 4.5% FTC) and cough increased (8.8% d4T; 14.0% FTC). There was also a statistically significant difference between treatment arms in the frequency of symptomatic hyperlactatemia/lactic acidosis and peripheral neuropathy. Seven subjects developed symptomatic hyperlactatemia/lactic acidosis, all of who were in the d4T arm. Peripheral neuropathy (defined as paresthesia, neuropathy, or peripheral neuritis) occurred in 66 subjects in the d4T arm (23.2%) and 28 subjects in the FTC treatment arm (9.8%). Through 48 weeks, 29% of subjects had severe or potentially life-threatening AEs in the d4T arm as compared with 22.0% of subjects in the FTC arm.

The overall incidence of Grade 3 or 4 laboratory abnormalities was similar between the 2 treatment arms during 48 weeks of treatment. Thirty-eight percent of subjects in the d4T treatment arm versus 34% of subjects in the FTC treatment arm experienced ≥ 1 Grade 3 or 4 laboratory abnormality during the study. With respect to the incidence of Grade 3 or 4 abnormalities, the treatment groups were comparable across laboratory parameters, with the exception of serum amylase, which was statistically higher with d4T as compared to FTC.

The proportion of subjects who experienced an SAE was similar between the 2 treatment arms during the first 24 weeks of the study (7% in the FTC treatment arm vs 9.5% in the d4T treatment arm). Through 48 weeks, 7% of the FTC arm versus 10.5% of the d4T arm experienced an SAE; the difference between treatment arms was not statistically significant. Two subjects died during the study. Both of these subjects received d4T as their randomized treatment.

**Conclusion**

- Emtricitabine had greater antiviral efficacy versus d4T at all time points, with a widening of differences between the arms for secondary efficacy endpoints over time and significantly fewer treatment-emergent mutations. Emtricitabine also had a favorable safety profile and lower tolerability failure over time compared with d4T in subjects with HIV-1 infection.

## 1.3. Study FTC-302

**Title**

A Randomized, Double Blind Equivalence Trial Comparing Emtricitabine to Lamivudine within a Triple Combination in Antiretroviral-Drug Naive HIV-1 Infected Patients

**Objective**

The primary objective of FTC-302 was to assess the safety and efficacy of FTC once daily as compared to twice-daily lamivudine when used within a BR containing d4T and a NNRTI (nevirapine or EFV).

**Study Design/Subject Population**

This supportive study was a Phase 3, randomized, double-blind (double-dummy), multicenter South African study to evaluate the equivalence of FTC to lamivudine in a triple drug combination therapy administered to ART-naive HIV-1 infected subjects. Eligible subjects were randomized in a 1:1 ratio (FTC 200 mg once daily: lamivudine 150 mg BID). The BR consisted of d4T (all subjects) plus either nevirapine (subjects with HIV-1 RNA ≤ 100,000 c/mL) or EFV for subjects with pretreatment HIV-1 RNA > 100,000 c/mL.

A total of 512 subjects were randomized and 468 received ≥ 1 dose of study medication (ITT population).

Further details on the design and results of this study are available in the FTC-302 Final CSR.

**Efficacy Results**

Overall, the FTC and lamivudine treatment groups were equivalent in terms of the percentage of subjects that were considered efficacy failures through 48 weeks. At Week 48, 20.5% of the subjects in the FTC treatment group were efficacy failures as compared to 19.2% in the lamivudine treatment group. The stratum-adjusted difference between treatment groups (FTC - lamivudine) was 1.8%, which yielded a stratum-adjusted 95% CI of −5.2% to 8.9%. Similar results were observed when the population included all randomized subjects (n = 512). The analysis of time to efficacy failure yielded results similar to the proportion of efficacy failures described above. The KM probability of efficacy failure at 48 weeks was 22.3% and 20.6%, respectively, in the FTC and lamivudine treatment groups. The 95% CI for the difference between treatment groups (−5.7% to 9.1%) supports the conclusion that FTC was equivalent to lamivudine with respect to the probability of efficacy failure through 48 weeks. In terms of the

proportion of subjects with HIV-1 RNA ≤ 50 c/mL at Week 48, the FTC treatment arm (60.2%) was equivalent to the lamivudine treatment arm (63.8%). The stratum-adjusted difference between treatment groups (FTC – lamivudine) was −3.8% yielding a 95% CI for the difference between treatment groups of −12.6% to 5.1%. The mean increase in percent CD4 cells was similar between the 2 treatment groups (9.4% FTC; 9.7% lamivudine).

**Virology Results**

Genotypic analysis of isolates obtained at time of failure showed a lower incidence of new genotypic mutations in the FTC arm (20/33, 60.6%) compared with the lamivudine arm (20/23, 86.9%).

**Safety Results**

The safety results demonstrated that the 2 study drugs (FTC and lamivudine) were well tolerated in adult ART-naive HIV-1 infected subjects. There were no clinically relevant differences between subjects receiving the FTC or lamivudine triple combination therapy in terms of adverse experience profile, tolerability, or laboratory parameters. The overall incidence of AEs, discontinuations due to AEs, and SAEs was similar in both treatment groups. Serious AEs occurred in 22% of FTC-treated subjects and 25% of those treated with lamivudine with no difference in the incidence by type of event. There were 10 deaths during the study (4 FTC; 6 lamivudine). Two of the deaths were secondary to liver failure and were considered to be probably associated with the use of nevirapine. The other deaths were considered unrelated to study medication, and in general, were consistent with HIV-associated complications.

In terms of different types of commonly reported AEs, the frequency was similar between groups with the exception of accidental injury, dizziness, and gastroenteritis, which showed a statistically significant increase in frequency among subjects given lamivudine. This finding is likely random since lamivudine is not known to produce these side effects. The frequency of Grade 3 or Grade 4 laboratory abnormalities was 31% in both groups with no clinically relevant differences by specific laboratory parameter. Notably, the incidence of Grade 3 or 4 ALT elevations was similar between subjects treated with FTC (11.5%) and subjects treated with lamivudine (15.0%).

A total of 66 subjects (29 FTC; 37 lamivudine) developed a Grade 3 or 4 hepatic abnormality. All of these subjects were in the nevirapine stratum (n = 385), resulting in an incidence of 17% across both treatment groups within the nevirapine stratum. The incidence of treatment-emergent Grade 3 or Grade 4 hepatic abnormalities was not statistically different between FTC (15%) and lamivudine (19%). The frequency of hepatic abnormalities was greater in women (20% female, 13% male; 95% CI −0.1%, 14.6%).

**Conclusion**

- The supportive Study FTC-302 demonstrated equivalent efficacy between FTC given once daily and lamivudine given BID as part of a triple drug combination regimen in treatment-naive HIV-1 infected subjects. FTC and lamivudine had an equivalent safety and tolerability profile.

## 1.4. Study FTC-303

### Title

A Randomized, Open-Label Equivalence Study of FTC Versus Lamivudine in Patients on a Stable Triple Antiretroviral Therapy Regimen Containing Lamivudine, Stavudine or Zidovudine, and a Protease Inhibitor or a Non-Nucleoside Reserve Transcriptase Inhibitor

### Objective

The primary objective of this study was to establish the equivalence of antiviral activity between FTC and lamivudine by comparing the proportion of randomized subjects at 48 weeks whose plasma HIV-1 RNA level remained ≤ 400 c/mL.

### Study Design/Subject Population

Study FTC-303 was a Phase 3, 48-week, open-label, randomized, parallel group, multicenter study to evaluate the equivalence in terms of safety and efficacy, of FTC to lamivudine in HIV-1 infected subjects. Subjects who met the entry criteria were randomized in a 2:1 (FTC: lamivudine) ratio. Subjects randomized to FTC were switched from lamivudine to FTC PO while continuing on their current background therapy. Subjects randomized to lamivudine continued on their current lamivudine-containing therapy.

Of 459 subjects randomized, 440 received ≥ 1 dose of study medication; these 440 subjects comprised the ITT population.

Further details on the design and results of this study are available in the FTC-303 Final CSR.

### Efficacy Results

Using a noncompleter equals failure analysis, the proportion of subjects with HIV-1 RNA ≤ 400 c/mL through 48 weeks of therapy was 73% in the FTC arm and 82% in the lamivudine arm. The stratum-adjusted difference between treatment groups (FTC minus lamivudine) was −5.8 % yielding a stratum adjusted 95% CI of −13.5 % to 1.8%. The lower limit of the CI was within the protocol's pre-defined criteria (−15%) to conclude the noninferiority of FTC to lamivudine. Similarly, using a noncompleter equals failure analysis, the proportion of subjects with HIV-1 RNA ≤ 50 c/mL through 48 weeks of therapy was 68% in the FTC arm and 75% in the lamivudine arm (stratum adjusted treatment difference of –4.7%, 95% CI of –13.0% to 3.5%). For each of these response endpoints, the difference was largely attributed to attrition from the study and not loss of virologic activity.

The mean increase from baseline in CD4 cells was 29 cells/mm$^3$ in the FTC group and 61 cells/mm$^3$ in the lamivudine group, (stratum-adjusted 95% CI of –66 to 6 cells/mm$^3$) with a corresponding mean increase in percent CD4 from baseline of 2.5% and 1.7%, respectively, (stratum-adjusted 95% CI of 0.0% to 1.6%).

In addition to the aforementioned endpoints, no remarkable differences between treatment groups were observed for a number of other secondary efficacy endpoints including the proportion of subjects that were considered efficacy failures.

**Pharmacokinetic Results**

The PK substudy in Study FTC-303 evaluated the steady-state plasma profiles and PK of FTC in HIV infected subjects receiving once daily dosing of 200 mg FTC in combination with other antiretrovirals including NRTIs, NNRTIs, and HIV PIs. Emtricitabine demonstrated desirable PK characteristics, ie, rapid oral absorption producing high plasma concentrations over a prolonged period. The mean trough (lowest) plasma concentration measured at steady state in each subject was 8-fold than the average in vitro $IC_{90}$ of HIV suppression. This high plasma exposure to FTC, along with the relatively long plasma half-life (approximately 8 hours), supports the once daily dosing regimen. In addition, the relatively small intersubject variabilities in FTC PK would provide consistent plasma exposure to FTC over a broad subject population.

**Safety Results**

There were no significant differences between the FTC and lamivudine treatment groups with respect to the overall incidence of AEs or the incidence of SAEs.

The majority of AEs were mild to moderate in severity. In the case of specific AEs, the incidence of most AEs was comparable between treatment groups with the exception of infection, headache, rhinitis, flu syndrome, and lymphadenopathy which had a higher incidence in the FTC treatment group.

There was a statistically significant difference between the treatment arms in terms of subjects who discontinued the study due to an AE. Thirteen FTC-treated subjects discontinued the study due to an AE compared to 1 subject in the lamivudine treatment group who died during the study. Notably, all subjects discontinuing FTC due to AEs had plasma HIV-1 RNA levels $< 50$ c/mL at the time of discontinuation. Of the 13 FTC-treated subjects who withdrew due to an AE, 10 did so for AEs that were mild or moderate in severity. In the study overall, 3% of subjects discontinued due to an AE.

When considering more objective measures of safety, specifically laboratory abnormalities, no remarkable differences in the incidence of Grade 3 or 4 events between the 2 treatment groups were observed.

**Conclusions**

- When subjects who were on a stable lamivudine-based regimen were randomized to switch to once daily FTC in combination with their same background medications or to stay on their original regimen, there was no significant difference in virologic activity, immunologic response, or safety between the FTC and lamivudine treatment groups.

## 1.5. Study FTC-203

### Title

An Open-Label Study of a Once Daily Dose of Emtricitabine in Combination with Other Antiretroviral Agents in HIV Infected Pediatric Subjects

### Objectives

The objectives of this study were as follows:

- To obtain long-term safety experience for ART regimens containing FTC in HIV-1 infected pediatric subjects.
- To obtain antiviral activity data for ART regimens containing FTC in HIV-1 infected pediatric subjects.
- To determine the steady-state FTC concentrations in HIV-1 infected pediatric subjects and, if necessary, to refine the dose of FTC to achieve plasma concentrations comparable to those in adults given 200 mg FTC once daily.

### Study Design/Subject Population

This multicenter, open-label, nonrandomized, Phase 2 clinical study was designed to evaluate the safety, antiretroviral activity and PK of FTC in combination with other antiretroviral agents in pediatric HIV infected subjects aged < 18 years old. A minimum of 8 subjects were to be enrolled into each of the following age groups (inclusive): 3 to 24 months (Age Group 1), 25 months to 6 years (Age Group 2), 7 to 12 years (Age Group 3), and 13 to 17 years (Age Group 4). Subjects who were ART-naive (ie, no or only very limited prior ART) received FTC 6 mg/kg once daily + d4T BID + LPV/r BID, and subjects who were ART-experienced had the lamivudine in their existing ART regimens replaced with FTC 6 mg/kg once daily.

A total of 117 subjects (72 ART-naive and 45 ART-experienced) were enrolled into this study and received ≥ 1 dose of FTC. The data from 1 presumed ART-naive subject without a confirmed HIV infection were censored and are not included in the safety and efficacy analyses. Thus, the ITT Population comprised data from 116 subjects, 71 ART-naive and 45 ART-experienced.

Further details on the design and results of this study are available in the FTC-203 Final Week 48 CSR.

### Efficacy Results

Based on the TLOVR algorithm, overall 89.7% (104/116) of the subjects achieved and/or maintained suppression of plasma HIV-1 RNA to ≤ 400 c/mL at Week 48, with 93.0% (66/71) in the naive stratum and 84.4% (38/45) of subjects in the experienced stratum. The proportion of subjects also achieving and/or maintaining suppression of plasma HIV-1 RNA to ≤ 50 c/mL at

Week 48 was 75.9% (88/116) overall, with 78.9% (56/71) in the naive stratum and 71.1% (32/45) in the experienced stratum. The incidence of TLOVR-defined virologic failure at Week 48 was 6.9% (8/116) overall, and 4.2% (3/71) in the naive stratum and 11.1% (5/45) in the experienced stratum.

Within the naive stratum, the proportion of subjects achieving and maintaining a plasma HIV-1 RNA viral load of ≤ 400 c/mL at Week 48 was generally consistent across the 3 applicable age groups, with values of 92.3% (12/13), 95.6% (43/45) and 84.6% (11/13) in Age Groups 1 to 3, respectively. The proportion of ART-naive subjects in these same age groups achieving complete suppression of HIV-1 RNA viral load to ≤ 50 c/mL at Week 48 were 69.2% (9/13), 82.2% (37/45) and 76.9% (10/13), respectively. With 1 subject classified as a virologic failure in each of the 3 applicable age groups, the incidence of TLOVR-defined virologic failure through Week 48 was low at 7.7%, 2.2% and 7.7% in Age Groups 1 to 3, respectively.

Within the experienced stratum, the numbers of subjects in Age Groups 1 and 4 were too small (N = 3 each) to be meaningful. However, the majority of ART-experienced subjects in Age Groups 2 and 3 maintained suppression of plasma HIV-1 RNA viral load at ≤ 400 c/mL through Week 48 as defined by the TLOVR algorithm, with values of 91.3% (21/23) and 81.3% (13/16), respectively. The majority of subjects in both age groups also maintained complete suppression of HIV-1 RNA viral load to ≤ 50 c/mL through Week 48, with values of 78.3% (18/23) and 75.0% (12/16), respectively. The incidence of TLOVR-defined virologic failure through Week 48 was 4.3% (1/23) in Age Group 2 and 12.5% (2/16) in Age Group 3.

Within the naive stratum, significant decreases in HIV-1 RNA viral load were achieved through Week 48 across all 3 applicable age groups. Using a LOCF analysis, the overall (all applicable age groups) median (range) change in absolute and percent CD4+ cell counts were +313 (-512 to +1521) cells/$mm^3$ and +10.8 (-4.6 to +33.8)% for ART-naive subjects and -59.5 (-945 to +712) cells/$mm^3$ and +2.7 (-10.8 to +12.6)% for ART-experienced subjects.

**Pharmacokinetic Results**

Pharmacokinetic data was evaluable in 34/36 subjects who provided 24-hour profiles: 13/16 subjects in Age Group 1, 9/68 subjects in Age Group 2, 9/29 subjects in Age Group 3 and 3/3 subjects in Age Group 4. All subjects in Age Groups 1 and 2 and 4 subjects in Age Group 3 received FTC solution. Five subjects in Age Group 3 and 3 subjects in Age Group 4 received FTC capsules. The mean (CV%) principal PK parameters by age group for subjects receiving FTC oral solution and capsules combined are presented below:

| Age Group | N | | $C_{max}$ (µg/mL) | $T_{max}$ (hr) | $C_{min}$ (µg/mL) | $AUC_{tau}$ (hr•µg/mL) | $t_{½}$ (hr) | CL/F (mL/min) | CL/F (mL/min/kg) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13 | Mean<br>CV% | 1.93<br>34 | 1.6<br>54 | 0.059<br>52 | 8.70<br>37 | 8.87<br>36 | 115<br>27 | 13.2<br>34 |
| 2 | 9 | Mean<br>CV% | 1.90<br>46 | 1.5<br>58 | 0.060<br>90 | 8.98<br>39 | 7.44<br>45 | 242<br>48 | 13.7<br>58 |
| 3 | 9 | Mean<br>CV% | 2.59<br>32 | 2.2<br>103 | 0.071<br>31 | 13.00<br>18 | 7.71<br>42 | 240<br>34 | 7.1<br>26 |
| 4 | 3 | Mean<br>CV% | 2.42<br>20 | 2.33<br>65 | 0.079<br>38 | 14.46<br>12 | 8.34<br>26 | 233<br>13 | 5.1<br>11 |

The mean (CV%) principal PK parameters by age group for subjects receiving FTC solution only are presented in the following table:

| Age Group | N | | $C_{max}$ (µg/mL) | $T_{max}$ (hr) | $C_{min}$ (µg/mL) | $AUC_{tau}$ (hr•µg/mL) | $t_{½}$ (hr) | CL/F (mL/min) | CL/F (mL/min/kg) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13 | Mean<br>CV% | 1.93<br>34 | 1.6<br>54 | 0.059<br>52 | 8.70<br>37 | 8.87<br>36 | 115<br>27 | 13.2<br>34 |
| 2 | 9 | Mean<br>CV% | 1.90<br>46 | 1.5<br>58 | 0.060<br>90 | 8.98<br>39 | 7.44<br>45 | 242<br>48 | 13.7<br>58 |
| 3 | 4 | Mean<br>CV% | 3.06<br>35 | 1.5<br>38 | 0.074<br>14 | 13.46<br>19 | 9.76<br>35 | 198<br>47 | 8.2<br>28 |

For the subjects in Age Group 3, the $AUC_{tau}$ values were similar whether the subjects received solution or capsules.

**Safety Results**

The safety analyses are based on data collected from all 116 subjects in the ITT Population. Overall time on study was a median 96 weeks, with ART-naive subjects completing a median (range) 96 (21 to 132) weeks on study and ART-experienced subjects completing a median (range) 102 (6 to 172) weeks on study.

The primary safety endpoint was tolerability failure (discontinuation due AE). The incidences of tolerability failure were 1.7% (2/116) at Week 48 and 2.6% (3/116) at the data cut-off. The AEs leading to subject discontinuation prior to Week 48 were anemia (ART-experienced subject) and pancreatitis (ART-naive subject), with a fatality in an ART-naive subject with acute myeloid leukemia reported after Week 48.

Overall, 24/116 (20.7%) subjects experienced ≥ 1 SAE, including 1 death, through the data cut-off. SAEs were reported by 19/71 (26.8%) ART-naive subjects and 5/45 (11.1%) ART-experienced subjects. The only specific SAEs that occurred in > 1 subject were pneumonia (7/116, 6.0%), hepatitis A (4/116, 3.4%), accidental injury and pharyngitis (each 3/116, 2.6%)

and pancreatitis (2/116, 1.7%). Three (2.6%) subjects had an SAE that was assessed as possibly or probably related to study drug; pancreatitis in 2 subjects and anemia in 1 subject. One death was reported; a [redacted] ART-naive subject died approximately 1 year after initiating treatment with study medications and shortly after she was diagnosed with acute myeloid leukemia. The Investigator assessed the leukemia as remotely related to her study medications and noted that there were no obvious contributors evident as to the cause of the leukemia and her resulting death.

Nearly all (113/116, 97.4%) subjects experienced ≥ 1 AE through the data cut-off. The body systems most frequently affected were: body as a whole (86.2%), respiratory (79.3%), digestive (70.7%), skin and appendages (69.0%), special senses (48.3%) and hemic and lymphatic (30.2%). All other body systems were affected in > 20% of subjects. With few exceptions, the incidence of reported AEs within a given body system was higher in the naive stratum. In ART-naive subjects (N = 71), the most frequent AEs reported were infection (85.9%), skin discoloration (54.9%), cough increased (46.5%), vomiting (42.3%), diarrhea (36.6%) and otitis media (36.6%). In ART-experienced subjects (N = 45), the most frequent AEs reported were infection (40.0%), cough increased (35.6%), fever (31.1%), rhinitis (28.9%) and otitis media (24.4%).

Hyperpigmentation of the skin was reported in 42 subjects, including 39/71 (54.9%) ART-naive subjects and 3/45 (6.7%) ART-experienced subjects. Hyperpigmentation usually affected the hands and/or the feet, in particular the palms and soles, and more rarely the nails, tongue, and lips. All of these skin discoloration events were asymptomatic and assessed as mild in severity, except 1 event that was assessed as moderate in severity. None of these events required the premature discontinuation of the subject or the interruption of study medications.

Anemia was reported as an AE in 12 subjects (10.3%) in Study FTC-203, including 6 (8.5%) ART-naive subjects and 6 (13.3%) ART-experienced subjects. One ART-experienced subject had anemia (Grade 3 low hemoglobin) that the Investigator assessed as an SAE and probably related to the use of FTC and unrelated to the subject's other ART medications that led to premature discontinuation from the study. None of the other events were considered severe or life-threatening, serious, or a reason to discontinue study medication.

Overall, half (58/116, 50.0%) of the subjects had ≥ 1 AE assessed by the Investigator as possibly or probably drug related. The incidence of drug-related AEs was about 3-fold higher in ART-naive subjects (48/71, 67.6%), as compared to ART-experienced subjects (10/45, 22.2%), but very few specific drug-related AEs were reported in ≥ 5% of subjects in either ART stratum. In ART-naive subjects (N = 71), the only drug-related AEs reported at ≥ 5% frequency were skin discoloration (53.5%) and vomiting (18.3%). In ART-experienced subjects (N = 45), the only drug-related AE reported at ≥ 5% frequency was leukopenia (6.7%).

Overall, 14/116 (12.1%) subjects had ≥ 1 severe or potentially life-threatening AE, including 8/71 (11.3%) ART-naive subjects and 6/45 (13.3%) ART-experienced subjects, through the data cut-off. In ART-naive subjects, the only severe or potentially life-threatening AE reported in > 1 subject was pneumonia, which was reported in 4 (5.6%) subjects. Severe or potentially life-threatening AEs reported in 1 ART-naive subject (each 1.4%) were: accidental injury,

gastroenteritis, leukemia (fatal), leukopenia, pancreatitis, pharyngitis and sinusitis. In ART-experienced subjects, the only severe or potentially life-threatening AE reported in > 1 subject was leukopenia, which was reported in 2 (4.4%) subjects. Severe or potentially life-threatening AEs reported in 1 ART-experienced subject (each 2.2%) were anemia, cellulitis, hepatitis and tooth caries.

Almost all (97.4%) subjects had ≥ 1 treatment emergent laboratory abnormality (Grade 1 to 4). However, treatment emergent Grade 3 or 4 laboratory abnormalities were reported in < 10% of the subjects. The most common Grade 3 or 4 abnormality was Grade 4 ALT in 4 subjects (all diagnosed as hepatitis A viral infections).

**Conclusions**

Efficacy:

- Emtricitabine, administered once daily in combination with other antiretroviral drugs, showed potent antiviral activity in both ART-naive and -experienced children, as measured by significant and sustained decreases in HIV-1 RNA viral load. Using the TLOVR algorithm, 93% of naive children and 84% of experienced children achieved and/or maintained suppression of plasma HIV-1 viral loads to ≤ 400 c/mL after 48 weeks of treatment, with 79% of naive children and 71% of experienced children also achieving or maintaining complete suppression to ≤ 50 c/mL. Comparable results were obtained using the original protocol specified ITT (non-completer = failure) analysis.

- Within each ART stratum, comparing the proportion of subjects achieving and/or maintaining suppression of HIV-1 RNA viral load to ≤ 400 and ≤ 50 c/mL, the observed antiviral activity is generally consistent across all age groups and regardless of FTC formulation.

- At Week 48, the incidence of TLOVR-defined virologic failure was low at 7% overall, 4% in the naive children and 11% in the experienced children.

- A positive immunological response was seen in naive children with median increases in both absolute and percent CD4+ cell count. In experienced children, notwithstanding a small decrease in median absolute CD4+ cell count, considering the natural, age-related decline in CD4+ cells as all children mature, the observed modest increase in percent CD4+ suggests the preservation of CD4+ cells.

Safety:

- Emtricitabine was well tolerated in this pediatric population, which ranged in age from approximately 4 months to 16 years. The safety profiles were similarly favorable regardless of age and FTC dosage form, raising no safety concerns for the oral solution formulation.

- The incidence of tolerability failure, which was the primary safety endpoint and defined as any AE resulting in the discontinuation of treatment with FTC, was low at 1.7% after 48 weeks on treatment and 2.6% through the data cut-off date (median time on study for all subjects = 96 weeks).

- Although nearly all (97%) of the children experienced ≥ 1 AE during the study, very few specific events considered by the investigator to be related to study drug were observed in ≥ 5% of children. In the naive stratum, the only drug-related AEs occurring in ≥ 5% of children were skin discoloration (54%) and vomiting (18%). In the experienced stratum, the only AE occurring in ≥ 5% of children was leukopenia (7%). The incidence of drug-related AEs overall was about 3-fold higher in naive children, compared to experienced children.

- While the overall incidence of FTC-related hyperpigmentation reported in these children is higher than that observed in 3 controlled Phase 3 studies of FTC in HIV infected adults, the presentation of these events is similar to that observed in adults, ie, it typically affects the hands and/or the feet, is nonserious and almost always of mild severity, and no worse than moderate severity.

Pharmacokinetics:

- The FTC exposure, expressed as $AUC_{tau}$, achieved in children receiving 6 mg/kg once daily of oral solution up to 200 mg once daily or in children > 33 kg receiving a 200 mg capsule once daily is similar to exposure achieved in adults receiving a dose of 200 mg once daily.

- The higher variability in PK in younger children compared to adults may be in part due to greater variability in drug clearance and in part due to difficulties in administering a solution formulation to young children.

- The safety, efficacy and PK results of this study, in conjunction with the lower bioavailability of the oral solution, support the pediatric dosing recommendations of:

  — FTC oral solution: 6 mg/kg once daily up to a maximum dose of 240 mg once daily.

  — FTC capsule: 1 × 200 mg capsule once daily for children > 33 kg.

## 1.6. Tabular Listing of Clinical FTC Studies

| Protocol No. | Type of Study | Study Objective(s) | Study Design | Key Inclusion Criteria of Subjects | No. of Subjects: Gender M/F: Mean Age (Range) | Treatment Details (Drug/Dose/Form/Route/ Frequency/Duration) | Study Status; Type of Report | Location of Study Report |
|---|---|---|---|---|---|---|---|---|
| FTC-301A (Synopsis) | Efficacy and safety | Randomized, double-blind, multicenter equivalence study in ART-naive subjects comparing safety and efficacy of FTC and d4T within a triple drug combination containing ddI and EFV | Randomized (1:1), double-blind, active-controlled equivalence study | HIV-1 infected, treatment-naive subjects | 571 subjects<br>Arm 1: 286<br>Males: 239<br>Females: 47<br>Mean Age: 35.8 years (18 to 67)<br>Arm 2: 285<br>Males: 246<br>Females: 39<br>Mean Age: 36.5 years (18 to 69) | 48 weeks: Last subject completed 48 weeks on 24 Oct 2002; all subjects subsequently rolled to an open-label FTC-containing regimen or an alternative regimen off study<br><br>Arm 1: FTC 200 mg once daily PO<br>or<br>Arm 2: d4T 40 mg BID PO if ≥ 60 kg; 30 mg BID PO if < 60 kg<br>Both arms: ddI 400 mg once daily PO if ≥ 60 kg; 250 mg once daily PO if < 60 kg and EFV 600 mg once daily PO | Study completed<br>Interim Week 48 CSR | 5.3.5.1 |

| Protocol No. | Type of Study | Study Objective(s) | Study Design | Key Inclusion Criteria of Subjects | No. of Subjects: Gender M/F: Mean Age (Range) | Treatment Details (Drug/Dose/Form/Route/ Frequency/Duration) | Study Status; Type of Report | Location of Study Report |
|---|---|---|---|---|---|---|---|---|
| FTC-302 (Synopsis) | Efficacy and safety | Comparison of the safety and efficacy of FTC and 3TC within a triple drug combination containing d4T and NVP+EFV | Randomized (2:1), open-label, active-controlled switch study | Adults, HIV-1 infected, treatment-naive | Total Arm 1 = 234<br>Males: 99<br>Females: 135<br>Mean Age: 33.1 years (18 to 59)<br>Total Arm 2 = 234<br>Males: 94<br>Females: 140<br>Mean Age: 32.1 years (18 to 63) | 48 weeks<br>Arm 1: FTC 200 mg once daily PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg and NVP 200 mg once daily PO for 14 days then 200 mg BID PO (n = 194) or EFV 600 mg once daily PO (n = 40)<br>Arm 2: 3TC 150 mg BID PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg BID and NVP 200 mg once daily PO for 14 days then 200 mg BID PO (n = 191) or EFV 600 mg once daily PO (n = 43) | Study completed<br>Final CSR | 5.3.5.1 |

| Protocol No. | Type of Study | Study Objective(s) | Study Design | Key Inclusion Criteria of Subjects | No. of Subjects: Gender M/F: Mean Age (Range) | Treatment Details (Drug/Dose/Form/Route/ Frequency/Duration) | Study Status; Type of Report | Location of Study Report |
|---|---|---|---|---|---|---|---|---|
| FTC-303 (Synopsis) | Efficacy and safety | Comparison of FTC to 3TC in HIV-1 infected subjects with HIV-1 RNA ≤ 400 c/mL on a stable (≥ 12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI | Randomized (2:1) open-label, multi-center equivalence study | Adult, HIV-1 infected, 3TC-experienced, stable HIV-1 RNA | Arm 1: 294<br>Males: 250<br>Females: 44<br>Mean Age: 41.7 years (22 to 70)Arm 2: 146<br>Males: 127<br>Females: 19<br>Mean Age: 42.6 years (23 to 80) | 48 weeks<br>Arm 1: subjects switch from 3TC to FTC PO while continuing on current background therapy, or<br>Arm 2: subjects continuing on current 3TC-containing regimen | Study completed<br>Final CSR | 5.3.5.1 |
| FTC-203 (Synopsis) | Efficacy and safety | To obtain antiviral activity and long-term safety data, and to determine the steady-state FTC concentrations in HIV-1 infected pediatric subjects | Multicenter, open-label, non-randomized study | Pediatric (≥ 3 months to ≤ 17 years), HIV-1 infected, either ART-naive or -experienced | 116 subjects<br>ART-naive: 71<br>Males: 37<br>Females: 34<br>Mean Age: 4.8 years (0.3 to 12.0)<br>ART-experienced: 45<br>Males: 18<br>Females: 27<br>Mean Age: 7.4 years (1.1 to 15.9) | FTC administered for initial 48 weeks and then until commercial availability, for as long as subject met protocol-specified virologic criteria<br>ART-naïve: FTC 6 mg/kg once daily +d4T BID + LPV/r BID<br>ART-experienced: 3TC replaced with FTC 6 mg/kg once daily in existing ART regimens | Study completed<br>Final Week 48 CSR | 5.3.5.2 |

3TC, lamivudine; ART, antiretroviral therapy; BID, twice daily; CSR, clinical study report; d4T, stavudine; ddI, didanosine; EFV, efavirenz; F, female; FTC, emtricitabine (Emtriva®); HIV-1, human immunodeficiency virus, type 1; LPV/r, lopinavir/ritonavir, coformulated; M, male; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PO, oral; RNA, ribonucleic acid; ZDV, zidovudine

**SECTION 2.7**
**CLINICAL SUMMARY**

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## SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# DESCOVY®
# (EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/ TENOFOVIR ALAFENAMIDE)

Gilead Sciences

24 June 2016

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ATP | Adult Treatment Panel |
| B2M | beta-2-microglobulin |
| BMD | bone mineral density |
| BMI | body mass index |
| CD4 | cluster determinant 4 |
| CG | Cockcroft-Gault |
| CKD | chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| COBI; C | cobicistat |
| CSR | clinical study report |
| C-telopeptide | type I collagen C-telopeptide |
| DVY | emtricitabine/tenofofovir alafenamide (coformulated; Descovy®) |
| DXA | dual-energy x-ray absorptiometry |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| ECG | electrocardiogram |
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| $eGFR_{CKD\text{-}EPI,\ creatinine}$ | estimated glomerular filtration rate calculated using the CKD-EPI serum creatinine method |
| $eGFR_{CKD\text{-}EPI,\ cysC}$ | estimated glomerular filtration rate calculated using the CKD-EPI serum cystatin C method |
| EVG; E | elvitegravir |
| F/TAF | emtricitabine/tenofofovir alafenamide (coformulated; Descovy®) |
| F/R/TAF | emtricitabine/rilpivirine/tenofofovir alafenamide (coformulated; Odefsey®) |
| FDA | Food and Drug Administration |
| $FEPO_4$ | fractional excretion of phosphate |
| FEUA | fractional excretion of uric acid |
| FTC; F | emtricitabine |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| GGT | gamma-glutamyltransferase |
| Gilead | Gilead Sciences |
| HDL | high-density lipoprotein |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| LDL | low-density lipoprotein |
| m | module |

| | |
|---|---|
| Max | maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | minimum |
| N or n | number of subjects in a population (N) or subset (n) |
| NCEP | National Cholesterol Education Program |
| NRTI | nucleoside reverse transcriptase inhibitor |
| ODE | emtricitabine/rilpivirine/tenofofovir alafenamide (coformulated; Odefsey®) |
| RMP | risk management plan |
| P1NP | procollagen type 1 N-terminal propeptide |
| PTH | parathyroid hormone |
| Q1, Q3 | first quartile, third quartile |
| RBC | red blood cell |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate |
| TmP/GFR | renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate |
| UACR | urine albumin to creatinine ratio |
| ULN | upper limit of normal |
| UPCR | urine protein to creatinine ratio |
| US | United States |

# 1. EXPOSURE TO THE DRUG

Data in this submission supports updates to the prescribing informations for Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), Descovy (DVY; emtricitabine/tenofovir alafenamide [F/TAF]), and Odefsey (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [F/R/TAF]. The provision of the Week 96 clinical study report (CSR) for Study GS-US-292-0112 is an additional pharmacovigilance activity (Category 4) in the GEN, DVY and ODE Risk Management Plans (RMPs) agreed during the original marketing authorisation applications.

Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) is an oral, once-daily, fixed-dose combination that provides a potent and well-tolerated regimen for the long-term treatment of patients infected with HIV-1. Genvoya contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC; F), and the nucleotide reverse transcriptase inhibitor TAF. Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States (US) on 05 November 2015 and in the European Union on 19 November 2015.

Descovy is an oral, once-daily, FDC that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients with HIV-1. DVY contains the nucleoside reverse transcriptase inhibitor FTC and the nucleotide reverse transcriptase inhibitor TAF. Descovy was first approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents (aged 12 years and older) in the US on 04 April 2016 and in the European Union on 21 April 2016.

Odefsey is once daily FDC that provides an effective and well-tolerated regimen for the long term treatment of patients infected with HIV-1. ODE contains the nucleoside reverse transcriptase inhibitor FTC, the non-nucleoside reverse transcriptase inhibitor rilpivirine (R, RPV) and the nucleotide reverse transcriptase inhibitor TAF. Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the European Union on 21 June 2016.

## 1.1. Overall Safety Evaluation Plan

### 1.1.1. Primary Safety Population

This submission provides additional safety data for HIV-infected adults with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] according to the Cockcroft Gault [CG] formula [$eGFR_{CG}$] of 30 to 69 mL/min) in Study GS-US-292-0112 (Table 1) with results through 96 weeks of treatment with GEN (primary endpoint at Week 24); data from Cohort 1 switch subjects (N = 242) are summarized herein and data from Cohort 2 antiretroviral (ARV) therapy (ART)-naive subjects (N = 6) are presented in the clinical study report (CSR) (GS-US-292-0112 Week 96).

**Table 1. Overview of Study GS-US-292-0112**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| HIV-Infected Adults with Mild to Moderate Renal Impairment ($eGFR_{CG}$ 30 to 69 mL/min) | | | | |
| GS-US-292-0112 | Phase 3, open-label, multicenter, multicohort study to evaluate the safety, efficacy, and tolerability of GEN | **GEN:**<br>Virologically Suppressed (N = 242)<br>ART Naive (N = 6)[b] | Week 96<br>efficacy and safety | **CSR:**<br>GS-US-292-0112 Week 96<br>**Narrative:**<br>Section 1.1.3 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of TAF containing regimen).
b Because only 6 ART naive subjects were enrolled in Study GS-US-292-0112, data for these subject are not summarized; however, these data are presented in the CSR.

### 1.1.2. Safety Assessments

Adverse events (AEs) in Study GS-US-292-0112 were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1. Adverse events described in text were treatment emergent and are referred to as AEs. The investigator was responsible for final review and confirmation of accuracy of events, relationship, and severity, documented by the signature on the electronic case report form.

Bone safety was assessed as follows:

- Fracture events were defined by the Gilead Sciences (Gilead) medical monitor prior to database lock, based on the Standardized MedDRA Query of osteoporosis/osteopenia; fractures of fingers and toes were excluded from summary presentations because they represent traumatic events and are not considered clinically significant

- Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry (DXA) scan

- The following bone laboratory parameters were assessed: procollagen type 1 N-terminal propeptide (P1NP), type I collagen C-terminal telopeptide (C-telopeptide), and parathyroid hormone (PTH)

Renal safety was assessed as follows:

- The following renal laboratory parameters were assessed: serum creatinine, eGFR, serum cystatin C, proteinuria by dipstick, urine protein to creatinine ratio (UPCR), urine albumin to creatinine ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, beta-2-microglobulin to creatinine ratio, ratio of maximum renal tubular phosphate reabsorption rate to glomerular filtration rate [TmP/GFR], urine fractional excretion of phosphate [$FEPO_4$], and urine fractional excretion of uric acid [FEUA])

Laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that required medical or surgical intervention or led to study drug interruption or discontinuation were recorded as AEs or serious adverse events (SAEs), if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiograms [ECGs], x-rays, vital signs) associated with signs and/or symptoms were recorded as AEs or SAEs if they met the definitions. Laboratory abnormalities were graded according to toxicity criteria specified in the respective study protocol.

## 1.1.3. Narratives of Safety Studies

| | |
|---|---|
| **Location:** | GS-US-292-0112 Week 96 |
| **Title:** | A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment |
| **Objectives:** | The primary objective of this study was as follows:<br>• To evaluate the effect of GEN on renal parameters at Week 24<br>The secondary objectives of this study were as follows:<br>• To evaluate the effect of GEN on renal parameters at Weeks 48, 96, and 144<br>• To measure the proportion of subjects achieving virologic response (HIV-1 RNA < 50 copies/mL, US Food and Drug Administration [FDA] snapshot algorithm) at Weeks 24, 48, 96, and 144<br>• To evaluate the safety and tolerability of GEN through 144 weeks of treatment |
| **Study Design and Subject Population:** | Subjects with a stable eGFRCG of 30 to 69 mL/min for 3 months prior to screening were enrolled into Cohort 1 if they were on ART and virologically suppressed, or Cohort 2 if they were ART-naive. Subjects in Cohort 1 switched treatment from their existing ARV regimen to GEN at baseline ("switch" subjects); subjects in Cohort 2 initiated ART with GEN. For analysis purposes, Cohort 1 switch subjects were also grouped by baseline eGFRCG (< 50 mL/min and ≥ 50 mL/min).<br>Of the 248 treated subjects (242 subjects in Cohort 1 and 6 subjects in Cohort 2), 89.1% (221 subjects) were still on study treatment at the time of the data cut date (215 subjects in Cohort 1 and 6 subjects in Cohort 2).<br>**Cohort 1 switch subjects:**<br>Baseline median (first quartile [Q1], third quartile [Q3]) CD4 cell count was 632 cells/μL (456, 811) and 97.5% of subjects had baseline HIV-1 RNA < 50 copies/mL. At baseline, median (Q1, Q3) eGFRCG was 55.6 mL/min (45.7, 62.4); 33.1% of subjects had eGFRCG < 50 mL/min; and 63.6% of subjects were in chronic kidney disease (CKD) Stage 3 (eGFRCG 30 to 59 mL/min). Incidence of the following were higher in subjects taking a tenofovir disoproxil fumarate (TDF)-containing regimen immediately prior to the first dose of GEN than in subjects without preswitch TDF use: clinically significant proteinuria (47.8% vs 31.7%), clinically significant albuminuria (55.6% vs 36.6%), and proteinuria by urinalysis (36.7% vs 25.0%); however, the median eGFRCG was similar between the 2 subgroups. |
| **Summary of Results and Conclusions:** | • Subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) who switched to GEN had no clinically significant change in eGFR, but had rapid and significant improvements in proteinuria, albuminuria, proximal renal tubular function, and BMD.<br>o No change in actual glomerular filtration rate was observed through 24 weeks of treatment.<br>o Significant improvements in proteinuria, albuminuria, and tubular proteinuria were observed as soon as 1 week after switching to GEN and persisting through Week 96. There were decreases from baseline in the incidence of clinically significant proteinuria (from 42.3% at baseline to 18.2% at Week 96) and clinically significant albuminuria (from 48.9% at baseline to 26.7% at Week 96).<br>o Switching to GEN resulted in improvements in BMD over 96 weeks for subjects receiving TDF at baseline, and no change in BMD for subjects receiving non-TDF-containing regimens at baseline. No fragility fractures were reported. |

| | |
|---|---|
| **Summary of Results and Conclusions (continued):** | • Most subjects with $eGFR_{CG}$ < 50 mL/min had stable eGFR and significant improvements in tubular function through 96 weeks after switching to once-daily GEN without dose-limiting AEs.<br>• Genvoya was well tolerated. The incidence of discontinuations due to renal AEs was low, and no AEs of proximal renal tubulopathy (or Fanconi Syndrome) were reported.<br>• Median changes from baseline in metabolic laboratory parameters at Week 96 demonstrated a trend toward increase in all parameters for subjects who received TDF at baseline and a trend toward decrease in most parameters for subjects who did not receive TDF at baseline. Otherwise, no notable changes from baseline in median values for hematology, clinical chemistry, or liver-related laboratory parameters were observed through Week 96, and the majority of reported laboratory abnormalities were Grade 1 or 2.<br>• Overall, 88.4% of subjects maintained virologic suppression (HIV-1 RNA < 50 copies/mL) through Week 96, and CD4 cell counts were stable. |

## 1.2. Overall Extent of Exposure

Disposition for subjects in Study GS-US-292-0112 is described in m2.7.3, Section 3.1.

### 1.2.1. Clinical Studies

Duration of exposure for subjects in Study GS-US-292-0112 is summarized in Table 2 and described in details in the CSR (GS-US-292-0112 Week 96, Section 11.1)

Median duration of exposure to study drug was 108.1 (107.3, 111.3) weeks for Cohort 1 switch subjects.

**Table 2. GS-US-292-0112: Duration of Exposure to Study Drug (Safety Analysis Set)**

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)** | **Total (N = 242)** |
| Total Exposure to Study Drug (Weeks) | | | |
| Mean (SD) | 97.4 (26.77) | 105.4 (24.68) | 102.8 (25.61) |
| Median | 107.7 | 108.3 | 108.1 |
| Q1, Q3 | 92.4, 108.8 | 107.9, 119.7 | 107.3, 111.3 |
| Min, Max | 7.0, 132.0 | 4.9, 133.1 | 4.9, 133.1 |

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)** | **Total (N = 242)** |
| Total Exposure to Study Drug | | | |
| ≥ 48 Weeks (336 Days) | 74 (92.5%) | 152 (93.8%) | 226 (93.4%) |
| ≥ 60 Weeks (420 Days) | 73 (91.3%) | 151 (93.2%) | 224 (92.6%) |
| ≥ 72 Weeks (504 Days) | 72 (90.0%) | 149 (92.0%) | 221 (91.3%) |
| ≥ 84 Weeks (588 Days) | 71 (88.8%) | 148 (91.4%) | 219 (90.5%) |
| ≥ 96 Weeks (672 Days) | 51 (63.8%) | 144 (88.9%) | 195 (80.6%) |
| ≥ 108 Weeks (756 Days) | 38 (47.5%) | 121 (74.7%) | 159 (65.7%) |
| ≥ 120 Weeks (840 Days) | 11 (13.8%) | 37 (22.8%) | 48 (19.8%) |
| ≥ 132 Weeks (924 Days) | 1 (1.3%) | 3 (1.9%) | 4 (1.7%) |

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.
The latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-Day Follow-up visit date) was used to impute the last dose date for subjects with the last dose date completely missing, with only year known, or for subjects still on study drug. If the last study drug end date was nonmissing, then it was used to impute the last dose date.
Source: Section 15.1, Table 6

### 1.2.2. Postmarketing Data

Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 05 November 2015. As of 30 April 2016, cumulative patient exposure to GEN is estimated to be 13,960 patient-years.

Descovy was first approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents (aged 12 years and older) in the US on 04 April 2016. As of 31 May 2016, cumulative patient exposure to DVY is estimated to be 2064 patient-years.

Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016. As of 31 May 2016, cumulative patient exposure to ODE is estimated to be 1638 patient-years.

## 1.3. Demographic and Other Characteristics

### 1.3.1. Demographic and General Baseline Characteristics

Demographic and general baseline characteristics of subjects in Study GS-US-292-0112 are described in detail in the CSR (GS-US-292-0112 Week 96, Section 8.3.1).

The majority of Cohort 1 switch subjects were male (79.3%). Median and mean age was 58 years (range: 24 to 82; Table 3). The most common races were white (62.8%), black (18.2%),

or Asian (14.0%), and most subjects were not Hispanic/Latino (86.4%). The median (Q1, Q3) body mass index (BMI) at baseline was 24.1 (21.4, 26.9) kg/m$^2$.

**Table 3. GS-US-292-0112: Demographic and Baseline Characteristics (Cohort 1, Safety Analysis Set)**

| Characteristic[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| Age (Years) | | | |
| Mean (SD) | 59 (10.0) | 57 (9.8) | 58 (9.9) |
| Median | 59 | 58 | 58 |
| Q1, Q3 | 52, 66 | 51, 64 | 52, 65 |
| Min, Max | 31, 82 | 24, 76 | 24, 82 |
| Sex (n, %) | | | |
| Male | 59 (73.8%) | 133 (82.1%) | 192 (79.3%) |
| Female | 21 (26.3%) | 29 (17.9%) | 50 (20.7%) |
| Race (n, %) | | | |
| American Indian or Alaska Native | 1 (1.3%) | 0 | 1 (0.4%) |
| Asian | 23 (28.8%) | 11 (6.8%) | 34 (14.0%) |
| Black | 14 (17.5%) | 30 (18.5%) | 44 (18.2%) |
| Native Hawaiian or Pacific Islander | 0 | 2 (1.2%) | 2 (0.8%) |
| White | 39 (48.8%) | 113 (69.8%) | 152 (62.8%) |
| Other | 3 (3.8%) | 4 (2.5%) | 7 (2.9%) |
| Not Permitted | 0 | 2 (1.2%) | 2 (0.8%) |
| Ethnicity (n, %) | | | |
| Hispanic or Latino | 12 (15.0%) | 19 (11.7%) | 31 (12.8%) |
| Not Hispanic or Latino | 68 (85.0%) | 141 (87.0%) | 209 (86.4%) |
| Not Permitted | 0 | 2 (1.2%) | 2 (0.8%) |
| Baseline Body Mass Index (kg/m$^2$) | | | |
| Mean (SD) | 22.9 (3.89) | 25.1 (4.05) | 24.4 (4.12) |
| Median | 22.9 | 24.9 | 24.1 |
| Q1, Q3 | 20.0, 25.1 | 22.1, 27.2 | 21.4, 26.9 |
| Min, Max | 15.7, 38.1 | 16.0, 39.8 | 15.7, 39.8 |

a The denominator for percentages is the number of subjects in the Safety Analysis Set.
Source: GS-US-292-0112 Week 96, Section 15.1, Table 3.1

### 1.3.2. Baseline Disease Characteristics

Baseline disease characteristics of subjects in Study GS-US-292-0112 are summarized by baseline $eGFR_{CG}$ in Table 4 and by preswitch TDF use in Table 5, and are described in detail in the CSR (GS-US-292-0112 Week 96, Section 8.3.2).

Of 242 Cohort 1 switch subjects treated, 39.3% had a medical history of hypertension and 13.6% had a medical history of diabetes (Table 4). Median (Q1, Q3) cluster determinant (CD4) cell count was 632 (456, 811) cells/µL, and the mean (SD) baseline CD4 cell count was 664 (286.4) cells/µL (range: 126 to 1813). Overall, 97.5% of subjects had baseline HIV-1 RNA < 50 copies/mL. The most common HIV risk factor categories were homosexual sex (52.1% of subjects) and heterosexual sex (40.9% of subjects). The majority of subjects (74.4%) had asymptomatic HIV-1 infection; 11.6% had symptomatic HIV-1 infection and 14.0% were diagnosed with AIDS.

The most common nonstudy-drug ARV medications received immediately prior to the first dose of study drug were NRTIs (73.6%), protease inhibitors (44.2%), and nonnucleoside reverse transcriptase inhibitors (26.9%). A total of 21.5% of subjects were on single-tablet regimens. Immediately prior to the first dose of study drug, 65.3% of subjects received a TDF-containing regimen (n = 158 subjects with preswitch TDF use; Table 5).

At baseline, the median (Q1, Q3) $eGFR_{CG}$ was 55.6 (45.7, 62.4) mL/min (Table 4). Overall, 33.1% of subjects had $eGFR_{CG}$ < 50 mL/min, 42.3% of subjects with nonmissing data (101 of 239) had clinically significant proteinuria (UPCR > 200 mg/g) at baseline, and 48.9% of subjects with nonmissing data (115 of 235) had clinically significant albuminuria (UACR ≥ 30 mg/g) at baseline. At baseline, 9.5% of subjects had Grade 2 proteinuria by urinalysis (dipstick), 23.1% of subjects had Grade 1 proteinuria, and 67.4% of subjects had no proteinuria. The majority of subjects were in CKD Stage 3 ($eGFR_{CG}$ 30 to 59 mL/min; 63.6%).

***Analysis by Preswitch TDF Use***

Median baseline $eGFR_{CG}$ was similar between Cohort 1 switch subjects with preswitch TDF use and those without preswitch TDF use, with median (Q1, Q3) values of 58.3 mL/min (48.0, 63.5) and 53.0 mL/min (43.1, 59.5), respectively (Table 5). The distribution of subjects who were in CKD Stage 2 or CKD Stage 3 differed between the 2 subgroups, with a lower percentage of Cohort 1 switch subjects with preswitch TDF use in CKD Stage 3 (57.6% versus 75.0%) and a higher percentage of these subjects in CKD Stage 2 (39.9% versus 23.8%) as compared with Cohort 1 switch subjects without preswitch TDF use.

The incidence of clinically significant proteinuria (UPCR > 200 mg/g), clinically significant albuminuria (UACR ≥ 30 mg/g), and proteinuria by urinalysis (any grade) was higher in Cohort 1 subjects with preswitch TDF use than it was in those without preswitch TDF use, as follows:

- Clinically significant proteinuria (UPCR > 200 mg/g): 47.8% (75 of 157 subjects) in subjects with preswitch TDF use versus 31.7% (26 of 82 subjects) in subjects without preswitch TDF use

- Clinically significant albuminuria (UACR ≥ 30 mg/g): 55.6% (85 of 153 subjects) in subjects with preswitch TDF use versus 36.6% (30 of 82 subjects) in subjects without preswitch TDF use

- Proteinuria by urinalysis (any grade): 36.7% (58 of 158 subjects) in subjects with preswitch TDF use versus 25.0% (21 of 84 subjects) in subjects without preswitch TDF use

**Table 4. GS-US-292-0112: Baseline Disease Characteristics (Cohort 1, Safety Analysis Set)**

| Characteristic[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)** | **Total (N = 242)** |
| HIV-1 RNA ($log_{10}$ copies/mL) | | | |
| N | 80 | 162 | 242 |
| Mean (SD) | 1.30 (0.103) | 1.33 (0.381) | 1.32 (0.318) |
| Median | 1.28 | 1.28 | 1.28 |
| Q1, Q3 | 1.28, 1.28 | 1.28, 1.28 | 1.28, 1.28 |
| Min, Max | 1.28, 1.94 | 1.28, 4.88 | 1.28, 4.88 |
| HIV-1 RNA Category (copies/mL) | | | |
| < 50 | 78 (97.5%) | 158 (97.5%) | 236 (97.5%) |
| ≥ 50 to ≤ 100,000 | 2 (2.5%) | 4 (2.5%) | 6 (2.5%) |
| > 100,000 to ≤ 400,000 | 0 | 0 | 0 |
| > 400,000 | 0 | 0 | 0 |
| CD4 Cell Count (/μL) | | | |
| N | 80 | 162 | 242 |
| Mean (SD) | 673 (326.5) | 660 (265.3) | 664 (286.4) |
| Median | 622 | 635 | 632 |
| Q1, Q3 | 449, 844 | 461, 797 | 456, 811 |
| Min, Max | 126, 1813 | 136, 1517 | 126, 1813 |
| CD4 Cell Count Category (/μL) | | | |
| < 50 | 0 | 0 | 0 |
| ≥ 50 to < 200 | 2 (2.5%) | 3 (1.9%) | 5 (2.1%) |
| ≥ 200 to < 350 | 8 (10.0%) | 11 (6.8%) | 19 (7.9%) |
| ≥ 350 to < 500 | 16 (20.0%) | 37 (22.8%) | 53 (21.9%) |
| ≥ 500 | 54 (67.5%) | 111 (68.5%) | 165 (68.2%) |

| Characteristic[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| CD4% | | | |
| N | 80 | 162 | 242 |
| Mean (SD) | 31.5 (9.53) | 34.7 (10.26) | 33.7 (10.11) |
| Median | 32.2 | 36.1 | 34.7 |
| Q1, Q3 | 25.4, 37.2 | 26.8, 42.3 | 26.4, 41.1 |
| Min, Max | 9.4, 51.7 | 13.5, 59.2 | 9.4, 59.2 |
| HIV Risk Factors[b] | | | |
| Heterosexual Sex | 42 (52.5%) | 57 (35.2%) | 99 (40.9%) |
| Homosexual Sex | 30 (37.5%) | 96 (59.3%) | 126 (52.1%) |
| IV Drug Use | 1 (1.3%) | 1 (0.6%) | 2 (0.8%) |
| Transfusion | 3 (3.8%) | 2 (1.2%) | 5 (2.1%) |
| Vertical Transmission | 0 | 0 | 0 |
| Unknown | 4 (5.0%) | 9 (5.6%) | 13 (5.4%) |
| Other | 1 (1.3%) | 1 (0.6%) | 2 (0.8%) |
| HIV Disease Status | | | |
| Asymptomatic | 46 (57.5%) | 134 (82.7%) | 180 (74.4%) |
| Symptomatic HIV Infections | 18 (22.5%) | 10 (6.2%) | 28 (11.6%) |
| AIDS | 16 (20.0%) | 18 (11.1%) | 34 (14.0%) |
| Renal-Related Medical History[b] | | | |
| Diabetes | 12 (15.0%) | 21 (13.0%) | 33 (13.6%) |
| Hypertension | 40 (50.0%) | 55 (34.0%) | 95 (39.3%) |
| Glomerulonephritis/Vasculitis | 1 (1.3%) | 1 (0.6%) | 2 (0.8%) |
| Interstitial Nephritis | 1 (1.3%) | 2 (1.2%) | 3 (1.2%) |
| Polycystic Kidney Disease | 1 (1.3%) | 3 (1.9%) | 4 (1.7%) |
| HIV Associated Nephropathy | 11 (13.8%) | 19 (11.7%) | 30 (12.4%) |
| Other | 34 (42.5%) | 91 (56.2%) | 125 (51.7%) |
| Clinically Significant Proteinuria (UPCR > 200 mg/g) | 45/80 (56.3%) | 56/159 (35.2%) | 101/239 (42.3%) |
| Clinically Significant Albuminuria (UACR ≥ 30 mg/g) | 48/75 (64.0%) | 67/160 (41.9%) | 115/235 (48.9%) |

| Characteristic[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| Proteinuria by Urinalysis | | | |
| Grade 0 | 45 (56.3%) | 118 (72.8%) | 163 (67.4%) |
| Grade 1 | 23 (28.8%) | 33 (20.4%) | 56 (23.1%) |
| Grade 2 | 12 (15.0%) | 11 (6.8%) | 23 (9.5%) |
| Grade 3 | 0 | 0 | 0 |
| $eGFR_{CG}$ by Category (mL/min) | | | |
| CKD Stage 1: ≥ 90 | 0 | 0 | 0 |
| CKD Stage 2: 60 to 89 | 0 | 83 (51.2%) | 83 (34.3%) |
| CKD Stage 3: 30 to 59 | 75 (93.8%) | 79 (48.8%) | 154 (63.6%) |
| CKD Stage 4: 15 to 29 | 5 (6.3%) | 0 | 5 (2.1%) |
| $eGFR_{CG}$ (mL/min) | | | |
| N | 80 | 162 | 242 |
| Mean (SD) | 41.5 (5.86) | 61.3 (7.38) | 54.8 (11.64) |
| Median | 42.6 | 60.3 | 55.6 |
| Q1, Q3 | 37.7, 45.7 | 55.5, 65.0 | 45.7, 62.4 |
| Min, Max | 26.2, 49.8 | 50.3, 89.7 | 26.2, 89.7 |
| $eGFR_{CKD\text{-}EPI,\ cysC}$ (mL/min/1.73 $m^2$), Adjusted for Age and Sex[c] | | | |
| N | 80 | 161 | 241 |
| Mean (SD) | 57.4 (18.08) | 76.9 (19.43) | 70.4 (21.07) |
| Median | 56.7 | 77.2 | 69.7 |
| Q1, Q3 | 44.6, 68.9 | 63.6, 89.5 | 55.9, 82.7 |
| Min, Max | 20.3, 107.2 | 26.5, 126.6 | 20.3, 126.6 |
| $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 $m^2$), Adjusted for Age and Sex, and Race | | | |
| N | 80 | 162 | 242 |
| Mean (SD) | 44.6 (11.91) | 59.5 (12.48) | 54.5 (14.14) |
| Median | 45.2 | 58.1 | 54.1 |
| Q1, Q3 | 38.2, 50.4 | 52.2, 65.6 | 46.0, 62.8 |
| Min, Max | 21.3, 94.4 | 32.6, 103.3 | 21.3, 103.3 |

a The denominator for percentages is the number of subjects in the Safety Analysis Set.
b A subject may fit more than 1 category of HIV risk factor or renal-related medical history; therefore, percentages may add to more than 100% for these 2 baseline characteristics.
c One subject had missing baseline $eGFR_{CKD\text{-}EPI,\ cysC}$ due to the baseline value having been collected on Day 2.
Source: GS-US-292-0112 Week 96, Section 15.1, Tables 4.1, 10.1.10.2, and 10.1.11.2

**Table 5. GS-US-292-0112: Selected Baseline Disease Characteristics by Preswitch TDF Use (Cohort 1, Safety Analysis Set)**

| Disease Characteristic[a] | Cohort 1: Switch (N = 242) | |
|---|---|---|
| | With Preswitch TDF Use (N = 158) | Without Preswitch TDF Use (N = 84) |
| Renal-Related Medical History[b] | | |
| Diabetes | 21 (13.3%) | 12 (14.3%) |
| Hypertension | 54 (34.2%) | 41 (48.8%) |
| Glomerulonephritis/Vasculitis | 1 (0.6%) | 1 (1.2%) |
| Interstitial Nephritis | 0 | 3 (3.6%) |
| Polycystic Kidney Disease | 2 (1.3%) | 2 (2.4%) |
| HIV Associated Nephropathy | 18 (11.4%) | 12 (14.3%) |
| Other | 89 (56.3%) | 36 (42.9%) |
| Clinically Significant Proteinuria (UPCR > 200 mg/g) | 75/157 (47.8%) | 26/82 (31.7%) |
| Clinically Significant Albuminuria (UACR ≥ 30 mg/g) | 85/153 (55.6%) | 30/82 (36.6%) |
| Proteinuria by Urinalysis | | |
| Grade 0 | 100 (63.3%) | 63 (75.0%) |
| Grade 1 | 43 (27.2%) | 13 (15.5%) |
| Grade 2 | 15 (9.5%) | 8 (9.5%) |
| Grade 3 | 0 | 0 |
| $eGFR_{CG}$ by Category (mL/min) | | |
| CKD Stage 1: ≥ 90 | 0 | 0 |
| CKD Stage 2: 60 to 89 | 63 (39.9%) | 20 (23.8%) |
| CKD Stage 3: 30 to 59 | 91 (57.6%) | 63 (75.0%) |
| CKD Stage 4: 15 to 29 | 4 (2.5%) | 1 (1.2%) |
| $eGFR_{CG}$ (mL/min) | | |
| Mean (SD) | 56.2 (11.49) | 52.1 (11.53) |
| Median | 58.3 | 53.0 |
| Q1, Q3 | 48.0, 63.5 | 43.1, 59.5 |
| Min, Max | 29.2, 88.6 | 26.2, 89.7 |

| Disease Characteristic[a] | Cohort 1: Switch (N = 242) | |
|---|---|---|
| | With Preswitch TDF Use (N = 158) | Without Preswitch TDF Use (N = 84) |
| $eGFR_{CKD\text{-}EPI,\ cysC}$ (mL/min/1.73 $m^2$), Adjusted for Age and Sex[c] | | |
| N | 157 | 84 |
| Mean (SD) | 74.7 (20.16) | 62.3 (20.46) |
| Median | 75.4 | 60.4 |
| Q1, Q3 | 60.9, 86.2 | 47.7, 75.0 |
| Min, Max | 26.5, 126.6 | 20.3, 110.8 |
| $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 $m^2$), Adjusted for Age, Sex, and Race | | |
| Mean (SD) | 57.5 (14.42) | 49.0 (11.85) |
| Median | 55.8 | 50.2 |
| Q1, Q3 | 48.9, 64.6 | 39.9, 55.8 |
| Min, Max | 24.9, 103.3 | 21.3, 71.4 |

a The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
b A subject may fit more than one category of renal-related medical history; therefore, percentages may add to more than 100% for this baseline characteristic.
c Subject [redacted] baseline $eGFR_{CKD\text{-}EPI,\ cysC}$ was missing due to baseline value collected on Day 2.
Source: GS-US-292-0112 Week 96, Section 15.1, Tables 4.2, 10.2.10.3, and 10.2.11.3

# 2. ADVERSE EVENTS

## 2.1. Analysis of Adverse Events

Adverse events for subjects in Study GS-US-292-0112 are described in detail in the CSR (GS-US-292-0112 Week 96, Section 11.3).

At least 1 AE was reported in 94.2% of Cohort 1 switch subjects (n = 228; baseline $eGFR_{CG}$ < 50 mL/min 95.0% [76 subjects]; baseline $eGFR_{CG} \geq 50$ mL/min 93.8% [152 subjects]; Table 6). Most AEs were Grade 1 or 2 in severity. Grade 3 or 4 AEs were reported in 14.9% of subjects (n = 36; baseline $eGFR_{CG}$ < 50 mL/min 12.5% [10 subjects]; baseline $eGFR_{CG} \geq 50$ mL/min 16.0% [26 subjects]). Adverse events considered related to study drug by the investigator were reported in 29.8% of subjects (n = 72; baseline $eGFR_{CG}$ < 50 mL/min 33.8% [27 subjects]; baseline $eGFR_{CG} \geq 50$ mL/min 27.8% [45 subjects]); of these, 3 subjects (1.2%) had Grade 3 or 4 AEs. Serious AEs were reported in 16.5% of subjects (n = 40; baseline $eGFR_{CG}$ < 50 mL/min 15.0% [12 subjects] baseline $eGFR_{CG} \geq 50$ mL/min 17.3% [28 subjects]). No SAE was considered related to study drug by the investigator. Adverse events leading to premature study drug discontinuation were reported in 5.0% of subjects (n = 12; baseline $eGFR_{CG}$ < 50 mL/min 10.0% [8 subjects]; baseline $eGFR_{CG} \geq 50$ mL/min 2.5% [4 subjects]); of these, 4 subjects (1.7%) discontinued due to AE(s) considered related to study drug by the investigator. One subject died during this study.

**Table 6. GS-US-292-0112: Overall Summary of Adverse Events (Cohort 1, Safety Analysis Set)**

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)** | **Baseline $eGFR_{CG} \geq 50$ mL/min (N = 162)** | **Total (N = 242)** |
| Subjects Experiencing Any AE | 76 (95.0%) | 152 (93.8%) | 228 (94.2%) |
| Subjects Experiencing Any Grade 2, 3, or 4 AE | 56 (70.0%) | 107 (66.0%) | 163 (67.4%) |
| Subjects Experiencing Any Grade 3 or 4 AE | 10 (12.5%) | 26 (16.0%) | 36 (14.9%) |
| Subjects Experiencing Any Study Drug-Related AE | 27 (33.8%) | 45 (27.8%) | 72 (29.8%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Study Drug-Related AE | 13 (16.3%) | 18 (11.1%) | 31 (12.8%) |
| Subjects Experiencing Any Grade 3 or 4 Study Drug-Related AE | 1 (1.3%) | 2 (1.2%) | 3 (1.2%) |
| Subjects Experiencing Any SAE | 12 (15.0%) | 28 (17.3%) | 40 (16.5%) |
| Subjects Experiencing Any Study Drug-Related SAE | 0 | 0 | 0 |
| Subjects Experiencing Any AE Leading to Premature Study Drug Discontinuation | 8 (10.0%) | 4 (2.5%) | 12 (5.0%) |
| Subjects Who Died | 0 | 1 (0.6%) | 1 (0.4%) |

Source: GS-US-292-0112 Week 96, Section 15.1, Table 12.1

### 2.1.1. Common Adverse Events

Adverse events for subjects with $eGFR_{CG}$ 30 to 69 mL/min (Study GS-US-292-0112) are described in detail in the CSR (GS-US-292-0112 Week 96, Section 11.3).

The following were the most commonly reported AEs in Cohort 1 switch subjects (Table 7): upper respiratory tract infection (13.6%, 33 subjects), diarrhea (13.2%, 32 subjects), and arthralgia (12.4%, 30 subjects).

Common AEs were consistent with those expected in the subject population, the known safety profile of GEN, or with previous clinical study experience with GEN in subjects with normal renal function.

The following AEs were reported for a notably lower percentage (> 2-fold percentage point difference) of subjects with baseline $eGFR_{CG}$ < 50 mL/min than with baseline $eGFR_{CG}$ ≥ 50 mL/min: upper respiratory tract infection (3.8% versus 18.5%), urinary tract infection (3.8% versus 9.3%), pain in extremity (5.0% versus 10.5%), and headache (2.5% versus 10.5%) (Table 7). The following AE was reported for a notably higher percentage (> 2-fold percentage point difference) of subjects with baseline $eGFR_{CG}$ < 50 mL/min than with baseline $eGFR_{CG}$ ≥ 50 mL/min: osteoporosis (7.5% versus 3.7%).

**Table 7. GS-US-292-0112: Adverse Events Reported for ≥ 5% of Subjects in Cohort 1 (Cohort 1, Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| Subjects Experiencing Any AE | 76 (95.0%) | 152 (93.8%) | 228 (94.2%) |
| Gastrointestinal Disorders | | | |
| Diarrhoea | 11 (13.8%) | 21 (13.0%) | 32 (13.2%) |
| Nausea | 6 (7.5%) | 15 (9.3%) | 21 (8.7%) |
| Constipation | 4 (5.0%) | 9 (5.6%) | 13 (5.4%) |
| General Disorders and Administration Site Conditions | | | |
| Fatigue | 5 (6.3%) | 12 (7.4%) | 17 (7.0%) |
| Infections and Infestations | | | |
| Upper Respiratory Tract Infection | 3 (3.8%) | 30 (18.5%) | 33 (13.6%) |
| Bronchitis | 8 (10.0%) | 19 (11.7%) | 27 (11.2%) |
| Nasopharyngitis | 4 (5.0%) | 15 (9.3%) | 19 (7.9%) |
| Urinary Tract Infection | 3 (3.8%) | 15 (9.3%) | 18 (7.4%) |
| Sinusitis | 3 (3.8%) | 12 (7.4%) | 15 (6.2%) |

| Adverse Events by System Organ Class and Preferred Term[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| Musculoskeletal and Connective Tissue Disorders | | | |
| Arthralgia | 7 (8.8%) | 23 (14.2%) | 30 (12.4%) |
| Back Pain | 5 (6.3%) | 19 (11.7%) | 24 (9.9%) |
| Osteopenia | 10 (12.5%) | 13 (8.0%) | 23 (9.5%) |
| Pain In Extremity | 4 (5.0%) | 17 (10.5%) | 21 (8.7%) |
| Myalgia | 4 (5.0%) | 9 (5.6%) | 13 (5.4%) |
| Osteoporosis | 6 (7.5%) | 6 (3.7%) | 12 (5.0%) |
| Nervous System Disorders | | | |
| Headache | 2 (2.5%) | 17 (10.5%) | 19 (7.9%) |
| Dizziness | 8 (10.0%) | 9 (5.6%) | 17 (7.0%) |
| Renal and Urinary Disorders | | | |
| Renal Cyst | 5 (6.3%) | 9 (5.6%) | 14 (5.8%) |
| Respiratory, Thoracic and Mediastinal Disorders | | | |
| Cough | 5 (6.3%) | 13 (8.0%) | 18 (7.4%) |
| Vascular Disorders | | | |
| Hypertension | 6 (7.5%) | 11 (6.8%) | 17 (7.0%) |

a Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: GS-US-292-0112 Week 96, Section 15.1, Table 12.2

### Adverse Events by Severity

Most AEs reported in Cohort 1 switch subjects (Study GS-US-292-0112) were Grade 1 or 2 in severity (Table 6). Grade 3 or 4 AEs were reported for 14.9% of Cohort 1 switch subjects (n = 36). The only Grade 3 or 4 AEs reported in > 1 subject were acute myocardial infarction (3 subjects); and acute kidney injury, dehydration, nephropathy, and weight decreased (2 subjects for each AE). All of these events were SAEs, with the exception of acute kidney injury in 1 subject, weight decreased in 1 subject, and both instances of nephropathy.

### Adverse Events Considered Related to Study Drug

The following were the most commonly reported AEs considered related to study drug by the investigator in Cohort 1 switch subjects (Table 8): diarrhea and dizziness (3.3%, 8 subjects for each AE); and headache, hypercholesterolemia, nausea, and osteopenia (2.1%, 5 subjects for each AE).

**Table 8. GS-US-292-0112: Study Drug-Related Adverse Events Reported for at Least 1% of Subjects in Cohort 1 (Cohort 1, Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term[a] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| Subjects Experiencing Any Study Drug-Related AE | 27 (33.8%) | 45 (27.8%) | 72 (29.8%) |
| Gastrointestinal Disorders | | | |
| Diarrhoea | 2 (2.5%) | 6 (3.7%) | 8 (3.3%) |
| Nausea | 2 (2.5%) | 3 (1.9%) | 5 (2.1%) |
| Constipation | 1 (1.3%) | 3 (1.9%) | 4 (1.7%) |
| Flatulence | 2 (2.5%) | 2 (1.2%) | 4 (1.7%) |
| Abdominal Discomfort | 2 (2.5%) | 1 (0.6%) | 3 (1.2%) |
| Dyspepsia | 0 | 3 (1.9%) | 3 (1.2%) |
| Metabolism and Nutrition Disorders | | | |
| Hypercholesterolaemia | 1 (1.3%) | 4 (2.5%) | 5 (2.1%) |
| Dyslipidaemia | 2 (2.5%) | 1 (0.6%) | 3 (1.2%) |
| Musculoskeletal and Connective Tissue Disorders | | | |
| Osteopenia | 3 (3.8%) | 2 (1.2%) | 5 (2.1%) |
| Nervous System Disorders | | | |
| Dizziness | 4 (5.0%) | 4 (2.5%) | 8 (3.3%) |
| Headache | 1 (1.3%) | 4 (2.5%) | 5 (2.1%) |
| Psychiatric Disorders | | | |
| Abnormal Dreams | 2 (2.5%) | 1 (0.6%) | 3 (1.2%) |
| Insomnia | 1 (1.3%) | 2 (1.2%) | 3 (1.2%) |

a Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: GS-US-292-0112 Week 96, Section 15.1, Table 12.5

### 2.1.2. Deaths

One Cohort 1 switch subject with baseline $eGFR_{CG} \geq 50$ mL/min died of cardiopulmonary arrest during the study (GS-US-292-0112 Week 96 CSR, Section 11.4). The event leading to death was considered unrelated to study drug by the investigator.

### 2.1.3. Other Serious Adverse Events

Serious AEs were reported in 16.5% of Cohort 1 switch subjects (n = 40), with similar percentages reported in subjects with baseline $eGFR_{CG} \geq 50$ mL/min (17.3%, n = 28) and $eGFR_{CG} < 50$ mL/min (15.0%, n = 12) (GS-US-292-0112 Week 96 CSR, Section 11.5).

The following SAEs were reported for > 1 subject: acute myocardial infarction (3 subjects), pneumonia (3 subjects), abdominal pain (2 subjects), cardiac failure congestive (2 subjects), dehydration (2 subjects), and syncope (2 subjects). All SAEs were considered unrelated to study drug by the investigator.

### 2.1.4. Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section.

Adverse events leading to study drug discontinuation were reported for 5.0% of Cohort 1 switch subjects (n = 12), with a higher percentage reported in subjects with baseline $eGFR_{CG}$ < 50 mL/min (10.0% [8 subjects]) compared with subjects with baseline $eGFR_{CG} \geq 50$ mL/min (2.5% [4 subjects]) (GS-US-292-0112 Week 96 CSR, Section 11.6). The only AE leading to study drug discontinuation reported in > 1 subject was nephropathy (3 subjects). All AEs leading to discontinuation of study drug were considered unrelated to study drug by the investigator, with the exception of those in 2 subjects with baseline $eGFR_{CG} < 50$ mL/min (sleep disorder and renal failure, respectively) and 2 subjects with baseline $eGFR_{CG} \geq 50$ mL/min (nephropathy and choking, respectively). Five subjects discontinued study drug due to renal AEs (Section 2.1.5.2.1).

### 2.1.5. Analysis of Adverse Events by Organ System or Syndrome

#### 2.1.5.1. Bone Safety

Bone safety for subjectsin Study GS-US-292-0112 is described in detail in the CSR (GS-US-292-0112 Week 96, Section 11.3.4.1).

##### 2.1.5.1.1. Fracture Events

Overall, 5 fracture events were reported in 4 Cohort 1 switch subjects (1.7%), of whom 3 were subjects with preswitch TDF use (1.9%) and 1 was a subject without preswitch TDF use (1.2%). One fracture event (spinal compression fracture) was reported as an SAE. All fracture AEs were the result of trauma and considered unrelated to study drug by the investigator; none were reported as fragility fractures and none resulted in discontinuation of study drug.

##### 2.1.5.1.2. Percentage Change from Baseline in Hip and Spine Bone Mineral Density

Overall, hip and spine BMD increased for Cohort 1 switch subjects after switching to GEN. Mean (SD) and median (Q1, Q3) percentage increases from baseline were observed in hip BMD (mean [SD]: 2.037% [4.2877]; median [Q1, Q3]: 1.780 [−0.409, 3.893]) and spine BMD (mean [SD]: 2.261% [4.9061]; median [Q1, Q3]: 2.079 [−0.185, 4.910]) at Week 96 (Table 9). The percentage changes from baseline in hip and spine BMD were statistically significant at each timepoint through Week 96 for Cohort 1 overall ($p < 0.001$).

There was evidence for an improvement in hip and spine BMD after switching to GEN, when assessed using a threshold of 3% for changes from baseline at Week 96 (Table 10); higher percentages of subjects had increases versus decreases from baseline in BMD at both hip (31.6% versus 6.5%) and spine (41.2% versus 10.6%).

***Analysis by Preswitch TDF Use***

Median (Q1, Q3) percentage increases from baseline in hip and spine BMD were observed at Week 96 in Cohort 1 switch subjects with preswitch TDF use, with no clinically significant changes from baseline in hip and spine BMD for Cohort 1 switch subjects without preswitch TDF use, as follows (Table 9):

- With preswitch TDF use
  - Hip BMD: 2.220% (0.586%, 4.474%)
  - Spine BMD: 2.834% (0.259%, 5.700%)
- Without preswitch TDF use
  - Hip BMD: 1.077% (−1.632%, 2.462%)
  - Spine BMD: 0.585% (−1.337%, 3.591%)

The percentage changes from baseline in hip and spine BMD were statistically significant at each timepoint through Week 96 for Cohort 1 switch subjects with preswitch TDF use ($p < 0.001$).

**Table 9. GS-US-292-0112: Changes from Baseline in Hip and Spine BMD at Week 96 (Cohort 1, Hip and Spine DXA Analysis Sets)**

| | Cohort 1: Switch | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | With Preswitch TDF Use (N = 154) | | | Without Preswitch TDF Use (N = 82) | | | Total (N = 236) | | |
| | N | Mean (SD) | Median (Q1, Q3) | N | Mean (SD) | Median (Q1, Q3) | N | Mean (SD) | Median (Q1, Q3) |
| Hip BMD[a] | | | | | | | | | |
| Baseline (g/cm$^2$) | 154 | 0.918 (0.1522) | 0.898 (0.803, 1.017) | 82 | 0.919 (0.1622) | 0.909 (0.800, 1.028) | 236 | 0.918 (0.1554) | 0.900 (0.803, 1.021) |
| % Change at Week 96 | 138 | 2.649 (4.4640) | 2.220 (0.586, 4.474) | 77 | 0.939 (3.7338) | 1.077 (−1.632, 2.462) | 215 | 2.037 (4.2877) | 1.780 (−0.409, 3.893) |
| Spine BMD[b] | | | | | | | | | |
| Baseline (g/cm$^2$) | 154 | 1.056 (0.1904) | 1.054 (0.897, 1.182) | 82 | 1.112 (0.1780) | 1.091 (0.986, 1.226) | 236 | 1.075 (0.1877) | 1.068 (0.938, 1.191) |
| % Change at Week 96 | 140 | 3.074 (4.9484) | 2.834 (0.259, 5.700) | 76 | 0.763 (4.4844) | 0.585 (−1.337, 3.591) | 216 | 2.261 (4.9061) | 2.079 (−0.185, 4.910) |

% Change = Change from baseline at a postbaseline visit / baseline × 100%

a Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.

b Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.

Source: GS-US-292-0112 Week 96, Section 15.1, Tables 20.1 and 20.2

**Table 10. GS-US-292-0112: Categorical Distribution of Changes > 3% in Hip and Spine BMD at Week 96 (Cohort 1, Hip and Spine DXA Analysis Sets)**

| | Cohort 1: Switch | | |
|---|---|---|---|
| | With Preswitch TDF Use n/N (%) | Without Preswitch TDF Use n/N (%) | Total n/N (%) |
| Percentage Changes in Hip BMD at Week 96[a] | | | |
| > 3% Decrease | 7/138 (5.1%) | 7/77 (9.1%) | 14/215 (6.5%) |
| No Decrease (≥ 0% Change) | 111/138 (80.4%) | 49/77 (63.6%) | 160/215 (74.4%) |
| > 3% Increase | 52/138 (37.7%) | 16/77 (20.8%) | 68/215 (31.6%) |
| Percentage Changes in Spine BMD at Week 96[b] | | | |
| > 3% Decrease | 10/140 (7.1%) | 13/76 (17.1%) | 23/216 (10.6%) |
| No Decrease (≥ 0% Change) | 110/140 (78.6%) | 45/76 (59.2%) | 155/216 (71.8%) |
| > 3% Increase | 68/140 (48.6%) | 21/76 (27.6%) | 89/216 (41.2%) |

a Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.
b Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.
Source: GS-US-292-0112 Week 96, Section 15.1, Tables 20.5 and 20.6

#### 2.1.5.1.3. Bone Laboratory Parameters

Data for C-telopeptide and P1NP are presented only through Week 48 because serum samples for these analyses were not collected thereafter.

A decrease from baseline in P1NP (bone formation) was observed in Cohort 1 switch subjects at Week 48 ($p < 0.001$). An increase from baseline in PTH was observed at Week 96 ($p = 0.001$). No clinically significant change from baseline was observed in C-telopeptide (bone resorption) at Week 48. Median (Q1, Q3) percentage changes from baseline in C-telopeptide and P1NP at Week 48, and in PTH at Week 96 were as follows:

- C-Telopeptide: −2.2% (−16.7%, 24.4%)
- P1NP: −25.29% (−45.98%, 2.00%)
- PTH: 5.1% (−23.5%, 47.3%)

***Analysis by Preswitch TDF Use***

For Cohort 1 switch subjects with preswitch TDF use, a decrease from baseline in P1NP was observed at Week 48, and no clinically significant changes from baseline in C-telopeptide at Week 48 or PTH at Weeks 48 or 96 were observed. For Cohort 1 switch subjects without preswitch TDF use, increases from baseline in C-telopeptide at Week 48 and PTH at Weeks 48 and 96 were observed, and no clinically significant change from baseline

was observed in P1NP at Week 48. Median (Q1, Q3) percentage changes from baseline in C-telopeptide and P1NP at Week 48, and in PTH at Week 96 were as follows:

- With preswitch TDF use:
  - C-Telopeptide: −5.8% (−19.4%, 12.1%)
  - P1NP: −35.03% (−49.84%, −18.35%)
  - PTH: −6.4% (−26.2%, 33.2%)
- Without preswitch TDF use:
  - C-Telopeptide: 14.3% (−9.6%, 30.6%)
  - P1NP: 0.95% (−16.86%, 31.41%)
  - PTH: 34.4% (−11.9%, 70.1%)

The percentage increases from baseline in C-telopeptide for Cohort 1 switch subjects without preswitch TDF use was statistically significant at Week 48 ($p < 0.001$), the percentage decrease from baseline in P1NP for Cohort 1 switch subjects with preswitch TDF use was statistically significant at Week 48 ($p < 0.001$), and the percentage increase from baseline in PTH was statistically significant at Weeks 48 and 96 for Cohort 1 switch subjects without preswitch TDF use ($p < 0.001$).

2.1.5.2. Renal Safety

Renal safety for subjects in Study GS-US-292-0112 is described in detail in the CSR (GS-US-292-0112 Week 96, Section 11.2).

2.1.5.2.1. Renal Events

There were no subjects with reported proximal tubulopathy (or Fanconi Syndrome).

Two Cohort 1 switch subjects (0.8%) had renal SAEs (both with baseline $eGFR_{CG} \geq 50$ mL/min). One subject had an SAE of Grade 2 urinary retention starting on Day 747 following outpatient cholecystectomy; the event was considered unrelated to study drug by the investigator and resolved after 1 day while study drug was continued. One subject had an SAE of Grade 3 acute renal failure starting on Day 17, which was considered unrelated to study drug by the investigator, but resulted in study drug interruption, and resolved 2 days after onset; the subject's serum creatinine values were below the baseline value (1.85 mg/dL) at each subsequent visit through Week 96.

Five Cohort 1 switch subjects (2.1%) had renal AEs that resulted in discontinuation of study drug: 3 subjects with baseline $eGFR_{CG} < 50$ mL/min (nephropathy, chronic kidney disease, and renal failure, respectively) and 2 subjects with baseline $eGFR_{CG} \geq 50$ mL/min (nephropathy in both subjects). Three of these events were considered unrelated to study drug by the investigator (nephropathy in 2 subjects, and CKD) and 2 were considered related to study drug by the investigator (nephropathy and renal failure).

2.1.5.2.2. Renal Laboratory Parameters

2.1.5.2.2.1. Serum Creatinine

Overall, there were no clinically significant changes from baseline in serum creatinine through Week 96 for Cohort 1 switch subjects, with no clinically significant differences in serum creatinine results based on baseline $eGFR_{CG}$ or preswitch TDF use. Overall median changes from baseline through Week 96 ranged from −0.03 to 0.04 mg/dL. Mean (SD) serum creatinine was 1.46 mg/dL (0.383) at baseline and 1.41 mg/dL (0.346) at Week 96, with a mean (SD) change from baseline of −0.03 mg/dL (0.279) at Week 96. The median (Q1, Q3) change from baseline in serum creatinine at Week 96 was −0.02 mg/dL (−0.17, 0.10); p = 0.075.

There were no clinically significant differences in the change from baseline in serum creatinine through Week 96 between Cohort 1 switch subjects with pre-switch TDF use and those without pre-switch TDF use. Mean (SD) and median (Q1, Q3) changes from baseline in serum creatinine at Week 96 were as follows:

- With pre-switch TDF use
  - Mean (SD): −0.05 mg/dL (0.289)
  - Median (Q1, Q3): −0.04 mg/dL (−0.20, 0.09); p = 0.011
- Without pre-switch TDF use
  - Mean (SD): 0.00 mg/dL (0.256)
  - Median (Q1, Q3): 0.02 mg/dL (−0.11, 0.13); p = 0.61

2.1.5.2.2.2. Estimated Glomerular Filtration Rate

Overall, there were no clinically significant changes from baseline in eGFR (regardless of filtration marker or equation) through Week 96 for Cohort 1 switch subjects. Overall, the ranges of median changes from baseline through Week 96 were as follows:

- $eGFR_{CG}$: −1.0 to 1.2 mL/min
- eGFR calculated using the CKD-EPI, serum cystatin C method ($eGFR_{CKD\text{-}EPI,\ CysC}$): 0.6 to 4.5 mL/min/1.73 $m^2$
- $eGFR_{CKD\text{-}EPI,\ creatinine}$: −2.1 to 0.6 mL/min/1.73 $m^2$

2.1.5.2.2.3. Serum Cystatin C

Overall, there were no clinically significant changes from baseline in serum cystatin C through Week 96 for Cohort 1 switch subjects. Overall median changes from baseline through Week 96 ranged from −0.05 to −0.01 mg/dL.

2.1.5.2.2.4. Serum Phosphorus

Overall, there were no clinically significant changes from baseline in serum phosphorus through Week 96 for Cohort 1 switch subjects. Overall median changes from baseline through Week 96 ranged from −0.1 to 0.3 mg/dL.

2.1.5.2.2.5. Proteinuria by Urinalysis (Dipstick)

Most Cohort 1 switch subjects had improvement from baseline (toxicity grade decreased at least 1 grade from baseline) in proteinuria toxicity grade at Week 96. The percentage and number of subjects with proteinuria grade improvements from baseline were as follows:

- Overall: 84.5% (60 of 71 subjects)
- Baseline $eGFR_{CG} < 50$ mL/min: 74.2% (23 of 31 subjects)
- Baseline $eGFR_{CG} \geq 50$ mL/min: 92.5% (37 of 40 subjects)

The percentage and number of subjects with proteinuria grade worsening from baseline were as follows:

- Overall: 4.1% (9 of 217 subjects)
- Baseline $eGFR_{CG} < 50$ mL/min: 5.7% (4 of 70 subjects)
- Baseline $eGFR_{CG} \geq 50$ mL/min: 3.4% (5 of 147 subjects)

***Analysis by Preswitch TDF Use***

Proteinuria grade improvements occurred in the majority of subjects irrespective of preswitch TDF use. Improvements from baseline in proteinuria toxicity grade were more common in subjects with preswitch TDF use than they were in those without preswitch TDF use; this difference was due to the higher incidence of proteinuria at baseline in Cohort 1 switch subjects with preswitch TDF use. The percentage and number of subjects with proteinuria grade improvements from baseline were as follows:

- With preswitch TDF use: 92.5% (49 of 53 subjects)
- Without preswitch TDF use: 61.1% (11 of 18 subjects)

The percentage and number of subjects with proteinuria grade worsening from baseline were as follows:

- With preswitch TDF use: 4.2% (6 of 144 subjects)
- Without preswitch TDF use: 4.1% (3 of 73 subjects)

2.1.5.2.2.6. Proteinuria by Quantitative Assessment

Decreases from baseline in median UPCR and UACR for Cohort 1 switch subjects with baseline $eGFR_{CG} < 50$ mL/min, those with baseline $eGFR_{CG} \geq 50$ mL/min, and for Cohort 1 overall were observed at Week 2 and persisted through Week 96.

Median (Q1, Q3) values and median (Q1, Q3) percentage changes from baseline for Cohort 1 switch subjects overall were as follows:

- UPCR
  - Baseline: 160.6 (73.1, 337.1) mg/g
  - Week 96: 86.7 (52.4, 153.0) mg/g; % change from baseline −37.7% (−65.1%, 7.5%)
- UACR
  - Baseline: 28.8 (7.9, 83.9) mg/g
  - Week 96: 10.6 (4.7, 35.1) mg/g; % change from baseline −45.5% (−77.3%, 13.6%)

Through Week 96, there were decreases from baseline in the incidence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) in Cohort 1 switch subjects with baseline $eGFR_{CG} < 50$ mL/min, in those with baseline $eGFR_{CG} \geq 50$ mL/min, and in Cohort 1 overall. For Cohort 1 switch subjects overall, the incidence of clinically significant proteinuria decreased from 42.3% at baseline to 18.2% at Week 96 and the incidence of clinically significant albuminuria decreased from 48.9% at baseline to 26.7% at Week 96.

***Analysis by Preswitch TDF Use***

Decreases from baseline in median UPCR and UACR for Cohort 1 switch subjects with preswitch TDF use were observed at Week 2 and persisted through Week 96. There were no significant changes from baseline in median UPCR or UACR for Cohort 1 switch subjects without preswitch TDF use. Median (Q1, Q3) values and median (Q1, Q3) percentage changes from baseline for Cohort 1 switch subjects were as follows:

With preswitch TDF use:

- UPCR
  - Baseline: 188.8 (90.7, 363.5) mg/g
  - Week 96: 81.3 (53.5, 126.3) mg/g; % change from baseline −47.4% (−72.2%, −12.2%)

- UACR
  - Baseline: 40.9 (10.3, 86.4) mg/g
  - Week 96: 9.8 (4.5, 29.0) mg/g; % change from baseline −63.2% (−82.1%, 0.5%)

Without preswitch TDF use:

- UPCR
  - Baseline: 104.5 (60.6, 282.3) mg/g
  - Week 96: 100.0 (48.8, 185.7) mg/g; % change from baseline −7.2% (−40.8%, 59.8%)
- UACR
  - Baseline: 18.0 (5.3, 64.9) mg/g
  - Week 96: 12.5 (5.1, 70.7) mg/g; % change from baseline −14.6% (−51.6%, 36.4%)

Through Week 96, there were decreases from baseline in the incidence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) both in Cohort 1 switch subjects with preswitch TDF use and in those without preswitch TDF use; however, only for Cohort 1 switch subjects with preswitch TDF use were the differences from baseline in the categorical distributions of UPCR and UACR values statistically significant at each timepoint through Week 96 ($p < 0.001$). For Cohort 1 switch subjects with preswitch TDF use, the incidence of clinically significant proteinuria decreased from 47.8% at baseline to 14.8% at Week 96 and the incidence of clinically significant albuminuria decreased from 55.6% at baseline to 24.5% at Week 96. For Cohort 1 switch subjects with preswitch TDF use, of those with clinically significant proteinuria at baseline, 69.7% (46 of 66 subjects) had no clinically significant proteinuria at Week 96 and of those with clinically significant albuminuria at baseline, 60.0% (45 of 75 subjects) had no clinically significant albuminuria at Week 96.

#### 2.1.5.2.2.7. Proximal Tubular Proteinuria Assessments

Decreases from baseline in median urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio for Cohort 1 switch subjects with baseline $eGFR_{CG} < 50$ mL/min, those with baseline $eGFR_{CG} \geq 50$ mL/min, and for Cohort 1 overall were observed at Week 2 and persisted through Week 96. Median (Q1, Q3) values and median (Q1, Q3) percentage changes from baseline for Cohort 1 switch subjects overall were as follows:

- Urine RBP to creatinine ratio
  - Baseline: 800.5 (129.9, 5099.9) µg/g
  - Week 96: 191.0 (87.7, 565.9) µg/g; % change from baseline −64.1% (−91.4%, 9.8%)

- Urine beta-2-microglobulin to creatinine ratio
  - Baseline: 1562.5 (218.1, 10,922.0) µg/g
  - Week 96: 201.6 (67.8, 838.5) µg/g; % change from baseline −83.6% (−96.4%, −31.1%)

***Analysis by Preswitch TDF Use***

Decreases from baseline in median (Q1, Q3) urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio for Cohort 1 switch subjects with preswitch TDF use were observed at Week 2 and persisted through Week 96 (Table 11). There were no significant changes from baseline in median urine RBP to creatinine ratio or urine beta-2-microglobulin to creatinine ratio for Cohort 1 switch subjects without preswitch TDF use.

**Table 11. GS-US-292-0112: Changes from Baseline in Urine RBP to Creatinine Ratio (µg/g) and Urine Beta-2-Microglobulin to Creatinine Ratio (µg/g) by Pre-Switch TDF Use (Cohort 1, Safety Analysis Set)**

| | Cohort 1: Switch (N = 242) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | With Pre-Switch TDF Use (N = 158) | | | | Without Pre-Switch TDF Use (N = 84) | | | |
| | N | Median (Q1, Q3) | N[a] | Median (Q1, Q3) % Change from Baseline | N | Median (Q1, Q3) | N[a] | Median (Q1, Q3) % Change from Baseline |
| Urine RBP to Creatinine Ratio Baseline | 157 | 1524.6 (249.6, 11,280.5) | — | — | 83 | 196.9 (84.9, 1483.0) | — | — |
| At Week 96 | 142 | 173.2 (90.2, 518.0) | 141 | −84.8 (−95.9, −42.8) | 72 | 245.8 (80.4, 853.6) | 71 | 10.0 (−51.6, 110.2) |
| Urine B2M to Creatinine Ratio Baseline | 156 | 3477.3 (557.3, 23,917.4) | — | — | 81 | 399.1 (80.7, 2636.4) | — | — |
| At Week 96 | 142 | 204.4 (78.0, 794.8) | 140 | −91.4 (−97.6, −61.8) | 72 | 168.6 (58.2, 919.6) | 70 | −35.3 (−82.6, 47.1) |

a Number of subjects with nonmissing values at baseline and the specified study visit.
Source: GS-US-292-0112, Section 15.1, Tables 10.2.8 and 10.2.9

#### 2.1.5.2.2.8. Other Renal Biomarkers

Overall there were no clinically significant changes from baseline in urine FEUA, TmP/GFR, or urine $FEPO_4$ for Cohort 1 switch subjects. The ranges of median changes from baseline through Week 96 were as follows:

- Urine FEUA: −2.0% to −0.3%
- TmP/GFR: −0.1 to 0.2 mg/dL
- Urine $FEPO_4$: −1.6% to 1.3%

***Analysis by Preswitch TDF Use***

A decrease from baseline in median (Q1, Q3) urine FEUA for Cohort 1 switch subjects with preswitch TDF use was observed at Week 2 and persisted through Week 96. There were no significant changes from baseline in median urine FEUA for Cohort 1 switch subjects without preswitch TDF use. Median (Q1, Q3) urine FEUA values and median (Q1, Q3) change from baseline at Week 96 for Cohort 1 switch subjects were as follows:

- With preswitch TDF use
  - Baseline: 10.0% (7.2%, 14.3%)
  - Week 96: 7.4% (5.3%, 9.6%); change from baseline −2.4% (−5.3%, −0.6%)
- Without preswitch TDF use
  - Baseline: 7.9% (5.3%, 10.8%)
  - Week 96: 7.2% (5.1%, 10.2%); change from baseline −0.3% (−1.7%, 1.5%)

## 2.2. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures, if applicable, are provided in the relevant CSRs.

# 3. CLINICAL LABORATORY EVALUATIONS

All laboratory abnormalities discussed in the following sections were treatment-emergent and are referred to as laboratory abnormalities.

## 3.1. Laboratory Abnormalities

Laboratory abnormalities for subjects in Study GS-US-292-0112 are described in detail in the CSR (GS-US-292-0112 Week 96, Section 11.7.3).

Through Week 96, at least 1 laboratory abnormality was reported in 99.6% of Cohort 1 switch subjects. The majority of laboratory abnormalities were Grade 1 or 2 in severity. The most commonly observed Grade 3 or 4 laboratory abnormalities were LDL (fasting) (28 subjects), total cholesterol (fasting, hypercholesterolemia) (18 subjects), serum glucose (nonfasting, hyperglycemia) (13 subjects), and creatine kinase (12 subjects; Table 12).

**Table 12. GS-US-292-0112: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Cohort 1 (Cohort 1, Safety Analysis Set)**

| Laboratory Panel, Laboratory Parameter, Grade[a,b] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| Maximum Postbaseline Toxicity Grade | 80 | 162 | 242 |
| Grade 3 or 4 | 37 (46.3%) | 54 (33.3%) | 91 (37.6%) |
| Chemistry | | | |
| ALT | 80 | 162 | 242 |
| Grade 3 or 4 | 1 (1.3%) | 5 (3.1%) | 6 (2.5%) |
| Amylase | 80 | 162 | 242 |
| Grade 3 or 4 | 6 (7.5%) | 4 (2.5%) | 10 (4.1%) |
| AST | 80 | 162 | 242 |
| Grade 3 or 4 | 1 (1.3%) | 3 (1.9%) | 4 (1.7%) |
| Creatine Kinase | 80 | 162 | 242 |
| Grade 3 or 4 | 6 (7.5%) | 6 (3.7%) | 12 (5.0%) |
| Creatinine | 80 | 162 | 242 |
| Grade 3 or 4 | 5 (6.3%) | 3 (1.9%) | 8 (3.3%) |
| GGT | 80 | 162 | 242 |
| Grade 3 or 4 | 2 (2.5%) | 3 (1.9%) | 5 (2.1%) |
| Lipase[c] | 19 | 20 | 39 |
| Grade 3 or 4 | 3 (15.8%) | 3 (15.0%) | 6 (15.4%) |
| Phosphate (Hypophosphatemia) | 80 | 162 | 242 |
| Grade 3 or 4 | 2 (2.5%) | 2 (1.2%) | 4 (1.7%) |
| Serum Glucose (Fasting, Hyperglycemia) | 80 | 162 | 242 |
| Grade 3 or 4 | 4 (5.0%) | 2 (1.2%) | 6 (2.5%) |
| Serum Glucose (Nonfasting, Hyperglycemia)[d] | 79 | 162 | 241 |
| Grade 3 or 4 | 7 (8.9%) | 6 (3.7%) | 13 (5.4%) |
| Total Cholesterol (Fasting, Hypercholesterolemia) | 75 | 157 | 232 |
| Grade 3 or 4 | 8 (10.7%) | 10 (6.4%) | 18 (7.8%) |
| Triglycerides (Fasting) | 75 | 157 | 232 |
| Grade 3 or 4 | 4 (5.3%) | 0 | 4 (1.7%) |

| Laboratory Panel, Laboratory Parameter, Grade[a,b] | Cohort 1: Switch | | |
|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) |
| LDL (Fasting) | 75 | 157 | 232 |
| Grade 3 or 4 | 8 (10.7%) | 20 (12.7%) | 28 (12.1%) |
| Uric Acid (Hyperuricemia) | 80 | 162 | 242 |
| Grade 3 or 4 | 3 (3.8%) | 2 (1.2%) | 5 (2.1%) |
| Urinalysis[e] | | | |
| Urine Glucose (Glycosuria) | 80 | 162 | 242 |
| Grade 3 | 5 (6.3%) | 5 (3.1%) | 10 (4.1%) |
| Urine Protein (Proteinuria) | 80 | 162 | 242 |
| Grade 3 | 2 (2.5%) | 1 (0.6%) | 3 (1.2%) |
| Urine RBC (Hematuria, Quantitative) | 80 | 162 | 242 |
| Grade 3 | 3 (3.8%) | 3 (1.9%) | 6 (2.5%) |

a Denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value (for the test).
b Subjects were counted once for the maximum postbaseline severity for each laboratory test.
c Lipase test was only performed for subjects with serum amylase > 1.5 × ULN.
d Nonfasting glucose was not collected at baseline; therefore, maximum postbaseline grade was summarized.
e For urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade was up to Grade 3.
Source: GS-US-292-0112 Week 96, Section 15.1, Table 14

## 3.2. Metabolic Laboratory Parameters

Metabolic laboratory parameters for subjects in Study GS-US-292-0112 are described in detail in the CSR (GS-US-292-0112 Week 96, Section 11.7.5).

For Cohort 1 switch subjects overall, statistically significant median increases from baseline to Week 96 were observed in fasting total cholesterol to high density lipoprotein (HDL) ratio and fasting triglycerides, but not in fasting total cholesterol, fasting direct low density lipoprotein (LDL) cholesterol, fasting HDL cholesterol, or fasting glucose (Table 13).

Based on the number of subjects with nonmissing data at Week 96, the following percentages of Cohort 1 switch subjects had categorical changes from baseline in the following NCEP ATP III lipid classifications (fasting results):

- Total cholesterol (< 200 mg/dL to ≥ 200 mg/dL): 33.0%, 35 of 106 subjects
- Direct LDL cholesterol (< 130 mg/dL to ≥ 130 mg/dL): 24.6%, 30 of 122 subjects
- HDL cholesterol (≥ 40 mg/dL to < 40 mg/dL): 11.2%, 21 of 187 subjects
- Triglycerides (< 200 mg/dL to ≥ 200 mg/dL): 19.5%, 30 of 154 subjects

### *Analysis by Preswitch TDF Use*

Cohort 1 switch subjects with preswitch TDF use were compared with those without preswitch TDF use for changes from baseline at Week 96 in fasting total cholesterol, fasting direct LDL cholesterol, fasting HDL cholesterol, fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose (Table 13). Generally, median changes from baseline at Week 96 demonstrated increases in subjects with preswitch TDF use and decreases for subjects without preswitch TDF use. For subjects who switched from a non-TDF-containing regimen, mean (SD) changes from baseline in fasting lipid laboratory parameters at Week 96 were as follows:

- Total cholesterol: −21 mg/dL (36.9)
- LDL cholesterol: −18 mg/dL (34.4)
- HDL cholesterol: −5 mg/dL (12.8)
- Triglycerides: 8 mg/dL (95.5)

The percentage of Cohort 1 switch subjects taking a lipid-modifying medication at study entry was lower in subjects with preswitch TDF use (42.4%, 67 subjects) than it was in those without preswitch TDF use (54.8%, 46 subjects). The percentage of Cohort 1 switch subjects initiating lipid-modifying medications during the study was similar between subjects with preswitch TDF use (24.1%, 38 subjects) and those without preswitch TDF use (23.8%, 20 subjects).

Fasting lipid parameters were also analyzed excluding subjects who were taking lipid-modifying medications. For subjects who switched from a non-TDF-containing regimen (excluding subjects taking lipid-modifying medications), mean (SD) changes from baseline in fasting lipid laboratory parameters at Week 96 were as follows:

- Total cholesterol: −10 mg/dL (27.7)
- LDL cholesterol: −12 mg/dL (31.5)
- HDL cholesterol: −4 mg/dL (13.9)
- Triglycerides: 15 mg/dL (110.4)

**Table 13. GS-US-292-0112: Changes from Baseline in Fasting Metabolic Assessments at Week 96 (Cohort 1, Safety Analysis Set)**

| | Cohort 1: Switch | | |
|---|---|---|---|
| | **With Preswitch TDF Use (N = 158)** | **Without Preswitch TDF Use (N = 84)** | **Total (N = 242)** |
| Total Cholesterol (mg/dL) | | | |
| Change at Week 96 | n = 142 | n = 73 | n = 215 |
| Median | 19 | −16 | 8 |
| Q1, Q3 | −2, 39 | −37, 3 | −19, 29 |
| P-value | **< 0.001** | **< 0.001** | 0.077 |
| Direct LDL Cholesterol (mg/dL) | | | |
| Change at Week 96 | n = 142 | n = 73 | n = 215 |
| Median | 9 | −14 | 3 |
| Q1, Q3 | −4, 28 | −36, 2 | −20, 23 |
| P-value | **< 0.001** | **< 0.001** | 0.37 |
| HDL Cholesterol (mg/dL) | | | |
| Change at Week 96 | n = 142 | n = 73 | n = 215 |
| Median | 1 | −4 | −1 |
| Q1, Q3 | −4, 6 | −13, 1 | −7, 5 |
| P-value | 0.46 | **< 0.001** | 0.072 |
| Total Cholesterol to HDL Cholesterol Ratio | | | |
| Change at Week 96 | n = 142 | n = 73 | n = 215 |
| Median | 0.2 | 0.0 | 0.2 |
| Q1, Q3 | −0.3, 0.8 | −0.5, 0.6 | −0.3, 0.6 |
| P-value | **< 0.001** | 0.76 | **0.003** |
| Triglycerides (mg/dL) | | | |
| Change at Week 96 | n = 142 | n = 73 | n = 215 |
| Median | 17 | 3 | 14 |
| Q1, Q3 | −24, 49 | −50, 46 | −33, 49 |
| P-value | **0.005** | 0.67 | **0.017** |
| Glucose (mg/dL) | | | |
| Change at Week 96 | n = 142 | n = 71 | n = 213 |
| Median | 2 | −2 | 0 |
| Q1, Q3 | −5, 11 | −11, 7 | −8, 10 |
| P-value | 0.12 | 0.35 | 0.51 |

P-value based on the 2-sided Wilcoxon signed rank test. Bolded p-values indicate a statistically significant difference ($p < 0.05$).
Source: GS-US-292-0112 Week 96, Section 15.1, Tables 18.1.1 to 18.1.5 and 18.3

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Detailed information on vital signs, physical findings, and other observations related to safety in Study GS-US-292-0112 may be found in the CSR (GS-US-292-0112 Week 96, Section 11.8). Results of safety ECG assessments are described in this section.

Among Cohort 1 switch subjects, clinically significant ECG abnormalities at Weeks 24, 48, and/or 96 were reported for 2.1% (n = 5; 2 with baseline $eGFR_{CG} < 50$ mL/min and 3 with baseline $eGFR_{CG} \geq 50$ mL/min). These abnormalities were reported as AEs considered unrelated to study drug by the investigator and did not result in study drug discontinuation.

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

Subgroup analyses of AE incidence were not conducted in Study GS-US-292-0112.

## 5.2. Extrinsic Factors

Subgroup analyses of AE incidence for extrinsic factors were not conducted in Study GS-US-292-0112.

## 5.3. Drug Interactions

No new information submitted.

## 5.4. Use in Pregnancy and Lactation

No pregnancies were reported in Study GS-US-292-0112 (GS-US-292-0112 Week 96 CSR, Section 11.9).

## 5.5. Overdose

No new safety issues have been identified regarding overdose since the original marketing application for GEN, DVY, or ODE.

## 5.6. Drug Abuse

No safety issues concerning the abuse or misuse of GEN, DVY, or ODE tablets are anticipated from the available data.

## 5.7. Withdrawal and Rebound

No new information is presented.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of GEN, DVY, or ODE on the ability to drive or operate machinery.

# 6. POSTMARKETING DATA

No postmarketing data are included in this submission.

# 7. REFERENCES

None.

# 8. APPENDIX

| Appendix Number | Appendix Title |
|---|---|
| 8.1 | Tabular Summary of Studies Relevant for Safety |

## 8.1. Tabular Summary of Studies Relevant for Safety

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population / Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | GS-US-292-0112 (synopsis) | Evaluate the effect of GEN on renal parameters | Phase 3, open-label, multicenter, multi-cohort study | GEN (E/C/F/TAF; 150/150/200/10 mg) QD PO | 144 weeks<br>Extension Phase: Subjects have option to continue study drug for another 48 weeks until GEN is commercially available, becomes available through an access program, or development is terminated | Enrolled: 252<br>Safety Analysis Set:<br>Cohort 1: 242<br>Cohort 2: 6<br>Continuing study drug at data cut date:<br>Cohort 1: 215<br>Cohort 2: 6 | HIV infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min<br>Cohort 1: ART-experienced<br>Cohort 2: ART-naive | Study ongoing; GS-US-292-0112 Week 96 Interim CSR |

**SECTION 2.7**
**CLINICAL SUMMARY**

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**SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY**

# DESCOVY®
# (EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

Gilead Sciences

25 July 2016

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| $CL_{cr}$ | creatinine clearance |
| COBI; C | cobicistat |
| CSR | clinical study report |
| DVY | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| ECG | electrocardiogram |
| EU | European Union |
| EVG; E | elvitegravir |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| FDC | fixed-dose combination |
| FTC; F | emtricitabine |
| FTC/RPV/TAF | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| HIV-1 | human immunodeficiency virus type 1 |
| LDL | low-density cholesterol |
| m | Module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| ODE | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| PK | pharmacokinetic(s) |
| RPV; R | rilpivirine |
| SAE | serious adverse event |
| SD | standard deviation |
| TAF | tenofovir alafenamide |
| TFV | tenofovir |
| US | United States (of America) |

## PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| $\lambda_z$ | terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug |
| $AUC_{inf}$ | area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$ |
| $AUC_{last}$ | area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration |

# 1. EXPOSURE TO THE DRUG

This submission supports proposed changes to the prescribing information for Descovy® (DVY; emtricitabine/tenofovir alafenamide [F/TAF]), Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), and Odefsey® (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]), based on new clinical pharmacology data from Study GS-US-320-1615, a Phase 1, open-label, single-dose study that evaluated the pharmacokinetics (PK) of tenofovir alafenamide (TAF) and its metabolite, tenofovir (TFV), in subjects with normal hepatic function and subjects with severe hepatic impairment.

Descovy is an oral, once-daily, fixed-dose combination (FDC) that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients with HIV-1. Descovy contains the nucleoside reverse transcriptase inhibitor emtricitabine (FTC; F) and the nucleotide reverse transcriptase inhibitor TAF. Descovy was first approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents (aged 12 years and older) in the United States (US) on 04 April 2016 (F/TAF 200/25 mg FDC) and in the European Union (EU) on 21 April 2016 (F/TAF 200/10 mg and 200/25 mg FDCs).

Genvoya is an oral, once-daily, FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, GEN contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG; E) and the pharmacoenhancer cobicistat (COBI; C). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 05 November 2015 and in the EU on 19 November 2015 (E/C/F/TAF 150/150/200/10 mg FDC in both regions).

Odefsey is another oral, once-daily, FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, ODE contains the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV; R). Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the EU on 21 June 2016 (FTC/RPV/TAF 200/25/25 mg FDC in both regions).

## 1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

Safety data are provided from the Phase 1 Study GS-US-320-1615 (Table 1), conducted to evaluate the PK of TAF and its metabolite, TFV, in subjects with normal hepatic function and subjects with severe hepatic impairment. All subjects received a single oral dose of TAF 25 mg on Day 1 and remained in-house until discharge on Day 7. A follow-up telephone call was made 10 to 14 days after study drug administration.

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18. Treatment-emergent AEs were defined as events with onset dates on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or events leading to premature discontinuation of study drug.

Laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that required medical or surgical intervention or led to study drug interruption, modification, or discontinuation were recorded as an AE, as well as a serious AE (SAE), if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram [ECG], x-rays, vital signs) that were associated with signs and/or symptoms were recorded as an AE or SAE if they met the definition of an AE or SAE as described in the clinical study protocol. Clinical laboratory results were graded according to criteria specified in the clinical study protocol.

Data from this study showed that TAF (administered as TAF 25-mg tablets) was safe and generally well tolerated when administered in subjects with normal or severely impaired hepatic function.

**Table 1. Phase 1 Study Supporting Clinical Safety**

| Safety Population | Study Included in Population | Number of Subjects Receiving TAF | CSR and Narrative Locations |
|---|---|---|---|
| TAF Phase 1 | GS-US-320-1615 (severe hepatic impairment and normal hepatic function) | 20 | **CSR:** GS-US-320-1615 **Narrative:** m2.7.2, Section 2.1 |

Narrative safety data from Study GS-US-320-1615 are presented in m2.7.2, Section 2.1, with a tabular summary in m2.7.2, Appendix 6.1.

## 1.2. Overall Extent of Exposure

A total of 20 subjects were enrolled in the study with 10 subjects in each of the treatment groups (ie, severe hepatic impairment and normal matched control). All 20 subjects received a single dose of TAF 25 mg and completed the study.

## 1.3. Demographics and Other Characteristics of Study Population

Demographic and baseline characteristics data for subjects in Study GS-US-320-1615 are described in the clinical study report (CSR) (GS-US-320-1615, Section 8.3).

Demographic and baseline characteristics were generally balanced between the 2 treatment groups. Most of the subjects were white (95.0%, 19 subjects) and non-Hispanic or Latino (65.0%, 13 subjects), and there was an even number of male and female subjects (50.0% in each group). Subjects had a mean (SD) age of 56 (8.2) years (range: 41-69 years), a mean (SD) body mass index of 27.9 (4.05) kg/$m^2$, a mean (SD) creatinine clearance ($CL_{cr}$) (Cockcroft-Gault) of 122.522 (30.755) mL/min, and a mean (SD) $CL_{cr}$ (Cockcroft-Gault – ideal body weight) of 96.962 (26.549) mL/min. All subjects were hepatitis B surface antigen negative.

# 2. ADVERSE EVENTS

All AEs were treatment-emergent and are referred to as AEs. All AEs for subjects in Study GS-US-320-1615 are described in detail in the CSR (GS-US-320-1615, Section 11.2).

## 2.1. Analysis of Adverse Events

Four subjects (40.0%) in the severe hepatic impairment group and 3 subjects (30.0%) in the normal matched control group had AEs (Table 2).

**Table 2. GS-US-320-1615: Overall Summary of Adverse Events (Safety Analysis)**

| | Severe Hepatic Impairment Group (N = 10) | Matched Normal Hepatic Function Group (N = 10) |
|---|---|---|
| Number of Subjects Experiencing | | |
| Treatment-Emergent AE | 4 (40.0%) | 3 (30.0%) |
| Grade 3 or 4 Treatment-Emergent AE | 1 (10.0%) | 0 |
| Treatment-Emergent AE Related to Study Drug | 1 (10.0%) | 2 (20.0%) |
| Treatment-Emergent SAE | 1 (10.0%) | 0 |
| Treatment-Emergent SAE Related to Study Drug | 0 | 0 |
| Treatment-Emergent AE Leading to Premature Study Drug Discontinuation | 0 | 0 |

Adverse events were mapped according to MedDRA, Version 18.
The most severe AE within a preferred term was counted for each subject by severity grade.
Source: GS-US-320-1615 CSR Section 15.1, Table 8

### 2.1.1. Common Adverse Events

Adverse events that occurred in at least 2 subjects in any group included mild (Grade 1) nausea and mild (Grade 1) headache (2 subjects each, both in the normal matched control group); all other AEs occurred in at most 1 subject per group.

Most AEs were mild (Grade 1) in severity with the exception of 1 moderate (Grade 2) event (AE of musculoskeletal chest pain) and 1 severe (Grade 3) event (SAE of hepatic failure), both in the severe hepatic impairment group; neither event was assessed by the investigator as being related to study drug. No subjects had life-threatening (Grade 4) AEs.

Adverse events considered by the investigator to be related to study drug included headache (1 subject in the severe hepatic impairment group and 2 subjects in the normal matched control group) and fatigue (1 subject in the normal matched control group). All of the AEs were mild (Grade 1) in severity and transient, resolving within 1 to 3 days.

### 2.1.2. Deaths

There were no deaths in Study GS-US-320-1615.

### 2.1.3. Other Serious Adverse Events

One SAE, considered unrelated to study drug by the investigator, was reported in Study GS-US-320-1615. A subject with severe hepatic impairment had an SAE of hepatic failure (reported term being hepatic decompensation) during the posttreatment follow-up phase of the study.

### 2.1.4. Other Significant Adverse Events

No subject in Study GS-US-320-1615 discontinued study drug due to an AE.

## 2.2. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, and pregnancies, if applicable, are provided in the relevant CSR.

# 3. CLINICAL LABORATORY EVALUATIONS

Clinical laboratory data for subjects in Study GS-US-320-1615 are described in detail in the CSR (GS-US-320-1615, Section 11.6).

All laboratory abnormalities were treatment-emergent and are referred to as laboratory abnormalities.

Most of the laboratory abnormalities were either Grade 1 or 2 in severity; no Grade 4 abnormalities occurred. Grade 3 laboratory abnormalities were observed in 2 subjects in the severe hepatic impairment group and 1 subject in the normal matched control group. One subject in the severe hepatic impairment group had Grade 3 glycosuria on Day 7; no subsequent results were available for this subject. This subject had a medical history of diabetes mellitus and a Grade 2 blood glucose level (240 mg/dL) on Day 7 coincident with the glycosuria finding. One subject in the severe hepatic impairment group had a Grade 3 high direct low-density lipoprotein (LDL) cholesterol level on Days 2, 3, and 7 (levels ranged from 323 to 337 mg/dL). This subject also had a Grade 3 high LDL cholesterol level (348 mg/dL) on Day −1. One subject in the normal matched control group had Grade 3 total cholesterol levels on Days 2, 3, and 7 (levels ranged from 304 to 319 mg/dL); this subject also had Grade 2 high LDL (271 mg/dL) on Day −1.

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs and ECG data for subjects in Study GS-US-320-1615 are described in detail in the CSR (GS-US-320-1615, Section 11.7).

## 4.1. Vital Signs

No clinically significant changes in vital signs occurred during Study GS-US-320-1615.

## 4.2. Electrocardiograms

No clinically significant changes in ECGs occurred during Study GS-US-320-1615.

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

In subjects with severe hepatic impairment in Study GS-US-320-1615 (m2.7.2, Section 2), total (bound and unbound) TAF exposure ($AUC_{last}$) was 49% lower in subjects with severe hepatic impairment relative to normal matched control subjects; however, due to an increase of free fraction (ie, as percent unbound TAF) in subjects with severe hepatic impairment, the free TAF exposure was comparable between the 2 study groups ($AUC_{last}$ of 41.7 ng•h/mL and $AUC_{inf}$ of 42.8 ng•h/mL in the severe hepatic impairment group vs $AUC_{last}$ of 46.0 ng•h/mL and $AUC_{inf}$ of 46.5 ng•h/mL in the normal matched control group). Accordingly, as the free TAF moiety is associated with therapeutic effect, no change in TAF efficacy is expected in patients with severe hepatic impairment.

In subjects with severe hepatic impairment, lower plasma exposures of TFV were observed in the severe hepatic impairment group compared with the normal matched control group. These changes were not considered clinically meaningful, as the overall TFV exposures were well below those observed following administration of tenofovir disoproxil fumarate. The percent unbound TFV was high in all subjects (> 95%) regardless of hepatic status.

## 5.2. Extrinsic Factors

No new information is submitted.

## 5.3. Drug Interactions

No new information is submitted.

## 5.4. Use in Pregnancy and Lactation

No pregnancies were reported in Study GS-US-320-1615 (GS-US-320-1615 CSR, Section 11.8).

## 5.5. Overdose

No new information is submitted.

## 5.6. Drug Abuse

No new information is submitted.

## 5.7. Withdrawal and Rebound

No new information is submitted.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No new information is submitted.

# 6. POSTMARKETING DATA

No new information is submitted.

# 7. REFERENCES

No references are included.

# 8. APPENDIX

No appendices are included.

**SECTION 2.7**
**CLINICAL SUMMARY**

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**SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY**

# DESCOVY®
# (EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

Gilead Sciences

01 August 2016

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| COBI, C | cobicistat |
| CSR | clinical study report |
| DVY | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| ECG | electrocardiogram |
| EE | ethinyl estradiol |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault method |
| EU | European Union |
| EVG, E | elvitegravir |
| FDC | fixed-dose combination |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| FTC, F | emtricitabine |
| FTC/RPV/TAF | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| m | module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NGM | norgestimate |
| ODE | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| RMP | risk management plan |
| RPV | rilpivirine |
| SAE | serious adverse event |
| TAF | tenofovir alafenamide |
| US | United States |

# 1. EXPOSURE TO THE DRUG

This submission supports proposed changes to the prescribing information for Descovy® (DVY, emtricitabine/tenofovir alafenamide [F/TAF]), Genvoya® (GEN, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), and Odefsey® (ODE, emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]), based on new clinical pharmacology data from Study GS-US-311-1790, a Phase 1, open-label study that evaluated the potential drug interaction between DVY and a representative oral contraceptive medication, in healthy female adult subjects. The provision of the final clinical study report (CSR) for Study GS-US-311-1790 is also an additional pharmacovigilance activity (Category 3) in the DVY Risk Management Plan (RMP) agreed during the original marketing authorization application.

Descovy is an oral, once-daily, fixed-dose combination (FDC) that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients infected with HIV-1. Descovy contains the nucleoside reverse transcriptase inhibitor emtricitabine (FTC, F) and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF). Descovy was first approved for the treatment of HIV-1 infection in combination with other ARV agents in adults and adolescents (aged 12 years and older) in the United States (US) on 04 April 2016 and in the European Union (EU) on 21 April 2016.

Genvoya is an oral, once-daily FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, GEN contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG, E) and the pharmacoenhancer cobicistat (COBI, C). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 05 November 2015 and in the EU on 19 November 2015.

Odefsey is another oral, once-daily FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, ODE contains the nonnucleoside reverse transcriptase inhibitor rilpivirine (RPV, R). Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the EU on 21 June 2016.

## 1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

Safety data are provided from Cohort 1 of Study GS-US-311-1790, a Phase 1, randomized, open-label study that evaluated the potential drug interaction between DVY (administered as the F/TAF 200/25 mg FDC) and a representative oral contraceptive medication, norgestimate (NGM)/ethinyl estradiol (EE), in healthy female adult subjects (Table 1).

**Table 1. Phase 1 Study Supporting Clinical Safety**

| Safety Population | Study Included in Population | Number of Subjects Receiving DVY | CSR and Narrative Locations |
|---|---|---|---|
| Phase 1<br>Healthy female adult subjects | GS-US-311-1790<br>(drug-drug interaction, DVY [F/TAF 200/25 mg FDC] and NGM/EE) | 15 (Cohort 1) | **CSR:**<br>GS-US-311-1790<br>**Narrative:**<br>m2.7.2, Section 2.1 |

Eligible subjects enrolled in Cohort 1 received study drug once daily in the morning with food according to the treatment schema in Table 2.

**Table 2. GS-US-311-1790: Treatment Schema**

| | Part A | Part B | | |
|---|---|---|---|---|
| | Lead-in | Cycle 1 | Cycle 2 | |
| **Study Day** | **L1-L28** | **1-28** | **29-42** | **43-56** |
| **Cycle Day** | **1-28** | **1-28** | **1-14** | **15-28** |
| NGM/EE[a] | X | X | X | X |
| DVY | — | — | X | — |

a During each 28-day cycle, each subject received 21 daily active tablets containing NGM/EE (Cycle Days 1-21) followed by 7 daily inactive tablets containing inert ingredients (Cycle Days 22-28).

Safety was assessed through monitoring of adverse events (AEs) and concomitant medications, clinical laboratory tests, electrocardiograms (ECGs), and periodic physical examinations, including vital signs.

Data from this study showed that administration of DVY (as the F/TAF 200/25 mg FDC) was safe and generally well tolerated in combination with a representative hormonal contraceptive medication, norgestimate (NGM)/ethinyl estradiol (EE), in healthy female adult subjects.

A narrative summary of the design and results from Study GS-US-311-1790 is presented in m2.7.2, Section 2.1, with a tabular summary in m2.7.2, Appendix 6.1.

### 1.2. Overall Extent of Exposure

Disposition for subjects in Study GS-US-311-1790 is described in the CSR (GS-US-311-1790, Section 8.1).

A total of 16 subjects were enrolled in Cohort 1 (DVY+NGM/EE) and received at least 1 dose of study drug. Fourteen subjects in Cohort 1 received all planned study treatments. Three subjects in Cohort 1 discontinued study drug early, as follows:

- One subject discontinued in Part A (Lead-in) due to a protocol violation; the last dose of study drug received was on Day L28. This subject received 1 cycle of NGM/EE and no DVY+NGM/EE.
- One subject withdrew consent in Cycle 1 of Part B; the last dose of study drug received was on Study Day 32. This subject received 2 cycles of NGM/EE and 4 days of DVY+NGM/EE.
- One subject was lost to follow up (did not return for follow-up visit on Day 56); the last dose of study drug received was on Study Day 43. This subject received 2 cycles of NGM/EE and 14 days of DVY+NGM/EE.

### 1.3. Demographic and Other Characteristics of Study Population

Study GS-US-311-1790 was conducted in healthy premenopausal female subjects, ages 24 to 45 years, inclusive. Demographic and other characteristics of the study population are summarized in the CSR (GS-US-311-1790, Section 8.3).

# 2. ADVERSE EVENTS

All adverse events (AEs) were treatment-emergent and are referred to as AEs. Only AEs occurring during Part B of the study are described here; AEs occurring during the Lead-in period (Part A) are presented in the CSR (GS-US-311-1790, Section 11.2).

## 2.1. Analysis of Adverse Events

Adverse events occurred in 86.7% of Cohort 1 subjects while receiving NGM/EE only and in 20.0% of Cohort 1 subjects while receiving DVY+NGM/EE (Table 3). Percentages of subjects with at least 1 AE considered by the investigator to be related to study drug were 73.3% while receiving NGM/EE only and 6.7% while receiving DVY+NGM/EE.

**Table 3. GS-US-311-1790: Overall Summary of Adverse Events, Part B (Safety Analysis Set)**

| | NGM/EE (N = 15) | DVY+NGM/EE (N = 15) | Total (N = 15) |
|---|---|---|---|
| Subjects Experiencing any AE | 13 (86.7%) | 3 (20.0%) | 13 (86.7%) |
| Subjects Experiencing any AE Related to Study Drug | 11 (73.3%) | 1 (6.7%) | 11 (73.3%) |

Adverse events were mapped according to Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0.
Only data from Part B is presented.
NGM/EE treatment summarized includes all of Part B Cycle 1, and Part B Cycle 2, Study Days 43-56.
Source: GS-US-311-1790 CSR, Section 15.1, Table 7

### 2.1.1. Common Adverse Events

The following AEs were reported in > 1 subject in Cohort 1 while receiving NGM/EE only: metrorrhagia (11 subjects, 73.3%), constipation (6 subjects, 40.0%), and headache (2 subjects, 13.3%). Constipation (2 subjects, 13.3%) was the only AE reported in > 1 subject while receiving DVY+NGM/EE.

The majority of AEs were Grade 1. One subject in Cohort 1 had a Grade 2 AE of right bundle branch block while receiving DVY+NGM/EE. This Grade 2 AE resolved while the subject was still on treatment and was considered unrelated to study drug by the investigator. There were no Grade 3 or 4 AEs.

The only AE considered related to study drug by the investigator that occurred in > 1 subject in either treatment group was metrorrhagia in 11 subjects (73.3%) while receiving NGM/EE only and in no subject while receiving DVY+NGM/EE.

### 2.1.2. Deaths

There were no deaths in Study GS-US-311-1790.

### 2.1.3. Other Serious Adverse Events

There were no serious adverse events (SAEs) reported in Study GS-US-311-1790.

### 2.1.4. Other Significant Adverse Events

2.1.4.1. Adverse Events Leading to Discontinuation of Study Drug

No subject in Study GS-US-311-1790 discontinued study drug due to an AE.

### 2.1.5. Analysis of Adverse Events by Organ System or Syndrome

No new information is submitted.

## 2.2. Narratives

No deaths, SAEs, AEs leading to discontinuation, or pregnancies occurred during Study GS-US-311-1790; therefore, no narratives are provided.

# 3. CLINICAL LABORATORY EVALUATIONS

All laboratory abnormalities were treatment-emergent and are referred to as laboratory abnormalities. Only laboratory abnormalities occurring in Part B of the study are summarized in this section; laboratory abnormalities reported in Part A are presented in the CSR (GS-US-311-1790, Section 11.6).

Laboratory abnormalities were reported in 12 subjects (87.0%) while receiving NGM/EE only and in 5 subjects (33.3%) while receiving DVY+NGM/EE. The most commonly reported laboratory abnormalities (any grade in > 1 subject while receiving the specified treatment) were occult blood in urine, hemoglobin decreased, phosphate decreased, sodium decreased, and urine protein. Most laboratory abnormalities were Grade 1. Grade 2 treatment-emergent laboratory abnormalities occurred in 4 subjects (26.7%) while receiving NGM/EE only and in no subject while receiving DVY+NGM/EE. Grade 3 laboratory abnormalities of occult blood in urine occurred in 1 subject (6.7%) while receiving NGM/EE only and 1 subject (6.7%) while receiving DVY+NGM/EE; both occurrences were linked to menses and neither occurrence was considered clinically significant. Grade 4 low lymphocytes occurred in 1 subject in this study at an unscheduled visit on Study Day 70, 14 days after the last dose of study drug; lymphocytes returned to normal on Study Day 84.

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs, physical findings, and other observations related to safety in the study are described in the CSR (GS-US-311-1790, Section 11.7).

## 4.1. Vital Signs

No clinically significant changes in vital signs (temperature, pulse, blood pressure, and respiration rate) occurred during Study GS-US-311-1790.

## 4.2. Electrocardiogram

One subject had clinically significant right bundle branch block and ST-T changes on electrocardiogram (ECG) on Study Day 33 while receiving DVY+NGM/EE. Both were reported as AEs, along with AEs of dizziness (Day 33) and noncardiac chest pain (Day 34). The overall ECG assessment was normal for this subject on Study Day 35 and the dizziness and noncardiac chest pain resolved on Study Day 37.

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

No new information is submitted.

## 5.2. Extrinsic Factors

No new information is submitted.

## 5.3. Drug Interactions

Drug-drug interaction results from Study GS-US-311-1790 are summarized in m2.7.2, Section 2.1. No clinically significant drug interactions between DVY and NGM/EE were observed in the healthy female adult subjects in the study.

## 5.4. Use in Pregnancy and Lactation

No new information is submitted.

## 5.5. Overdose

No new information is submitted.

## 5.6. Drug Abuse

No new information is submitted.

## 5.7. Withdrawal and Rebound

No new information is submitted.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No new information is submitted.

# 6. POSTMARKETING DATA

No new information is submitted.

# 7. REFERENCES

No references are included.

# 8. APPENDIX

No appendices are included.

**SECTION 2.7**
**CLINICAL SUMMARY**

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## SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)
# SUBMISSION REF. NO. : ODE-16-080
# (STUDY GS-US-366-1160)

Gilead Sciences

17 October 2016

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| β2M | beta-2-microglobulin |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| ATR | efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®) |
| BMD | bone mineral density |
| BMI | body mass index |
| CD4 | cluster determinant 4 |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CSR | clinical study report |
| CTx | C-terminal telopeptide |
| DDI | drug-drug interaction |
| DXA | dual-energy x-ray absorptiometry |
| ECG | electrocardiogram |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| FTC | emtricitabine (Emtriva®) |
| Gilead | Gilead Sciences |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| IV | intravenous |
| LDL | low-density lipoprotein |
| LSM | least-squares mean |
| m | Module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | not applicable |
| N or n | number of subjects in a population (N) or subset (n) |
| ODE | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| P1NP | procollagen type 1 N-terminal propeptide |
| PT | preferred term |
| PTH | parathyroid hormone |
| Q1, Q3 | first quartile, third quartile |
| RBC | red blood cell |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |

| | |
|---|---|
| RPV | rilpivirine |
| SAE | serious adverse event |
| SD | standard deviation |
| SOC | system organ class |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| UACR | urine albumin to creatinine ratio |
| ULN | upper limit of normal |
| UPCR | urine protein to creatinine ratio |
| US | United States |
| vs | versus |

# 1. EXPOSURE TO THE DRUG

Odefsey® (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]) is an oral, once-daily, fixed-dose combination that provides an effective and complete option for the long-term treatment of patients infected with HIV-1. Odefsey contains the nucleoside reverse transcriptase inhibitor FTC, the non-nucleoside reverse transcriptase inhibitor RPV, and the nucleotide reverse transcriptase inhibitor TAF. Odefsey was approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States (US) on 01 March 2016 and in the European Union on 21 June 2016.

Data in this document support updates to the product information for ODE. See also Module 2.7.3 Summary of Clinical Efficacy for Study GS-US-366-1216 which is also provided in this grouped application.

## 1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

### 1.1.1. Primary Safety Population for Odefsey

This document provides additional safety data for HIV-infected, virologically suppressed adults who switched treatment to ODE from the following (Table 1):

- Efavirenz/FTC/TDF (Atripla® [ATR]) (Study GS-US-366-1160): results through 48 weeks of treatment (primary endpoint at 48 weeks)

Data were not pooled across studies GS-US-366-1216 and GS-US-366-1160 due to the different prior treatment regimens evaluated. Across studies, data from a total of 754 subjects who received ODE are summarized (see below for Study GS-US-366-1160 and Module 2.7.3 Summary of Clinical Efficacy for Study GS-US-366-1216), with the following median (first quartile [Q1], third quartile [Q3]) durations of exposure to ODE:

- Study GS-US-366-1216: 47.9 (43.7, 59.1) weeks (N = 316)
- Study GS-US-366-1160: 47.9 (43.4, 59.1) weeks (N = 438)

## Table 1. Studies Supporting Clinical Safety

| Study | Study Design | Number of Subjects[a] by Treatment Regimens | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| **HIV-Infected, Virologically Suppressed Adults** | | | | |
| GS-US-366-1160 | Phase 3b randomized, double-blind, multicenter study to evaluate the efficacy, safety, and tolerability of switching to ODE from ATR | Switch to ODE (N = 438)<br>Stay on ATR (N = 437) | Week 48 efficacy and safety | **CSR:**<br>GS-US-366-1160 Week 48<br>**Narrative:**<br>m2.7.3, Section 2 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

### 1.1.2. Safety Assessments

Safety assessments for Study GS-US-366-1160 are described in this section.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0. Adverse events described in text were treatment-emergent and are referred to as AEs. The investigator was responsible for final review and confirmation of accuracy of events, relationship, and severity, documented by the signature on the electronic case report form.

Bone safety was assessed as follows:

- Fracture events were reviewed by the Gilead Sciences (Gilead) medical monitors prior to database lock, based on the Standardized MedDRA Query of osteoporosis/osteopenia and the MedDRA high-level group term of fractures for Study GS-US-366-1160
- Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry (DXA) scan
- The following bone laboratory parameters were assessed: procollagen type 1 N-terminal propeptide (P1NP), type I collagen C-terminal telopeptide (CTx), and parathyroid hormone (PTH)

The following renal laboratory parameters were assessed: serum creatinine, estimated glomerular filtration rate, proteinuria by dipstick, urine protein to creatinine ratio (UPCR), urine albumin to creatinine ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, and beta-2-microglobulin (β2M) to creatinine ratio.

Laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that required medical or surgical intervention or led to study drug interruption, modification or discontinuation were recorded as AEs or SAEs, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiograms [ECGs], x-rays, vital signs) associated with signs and/or symptoms were recorded as AEs or SAEs if they met the definitions. Laboratory abnormalities were graded according to toxicity criteria specified in the respective study protocol.

### 1.1.3. Narratives of Safety Studies

Narrative safety data from Study GS-US-366-1160 is presented in m2.7.3, Section 2.1.

## 1.2. Overall Extent of Exposure

Disposition for subjects in Study GS-US-366-1160 is described in m2.7.3, Section 3.1.

### 1.2.1. Clinical Studies

Duration of exposure for subjects in Study GS-US-366-1160 is summarized in Table 2 and described in detail in the CSR (Study GS-US-366-1160 Week 48, Section 11.1).

Median (Q1, Q3) duration of exposure to study drug was 47.9 (43.4, 59.1) weeks in the ODE group and 48.0 (43.4, 59.9) weeks in the ATR group.

**Table 2. GS-US-366-1160: Duration of Exposure to Study Drug (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) |
|---|---|---|
| Total Exposure to Study Drug (Weeks) | | |
| N | 438 | 437 |
| Mean (SD) | 47.9 (11.49) | 48.7 (11.67) |
| Median | 47.9 | 48.0 |
| Q1, Q3 | 43.4, 59.1 | 43.4, 59.9 |
| Min, Max | 0.7, 72.4 | 0.1, 72.7 |
| Total Exposure to Study Drug | | |
| >= 4 Weeks (28 days) | 435 (99.3%) | 431 (98.6%) |
| >= 8 Weeks (56 days) | 433 (98.9%) | 428 (97.9%) |
| >= 12 Weeks (84 days) | 431 (98.4%) | 425 (97.3%) |
| >= 24 Weeks (168 days) | 417 (95.2%) | 421 (96.3%) |
| >= 36 Weeks (252 days) | 406 (92.7%) | 415 (95.0%) |
| >= 48 Weeks (336 days) | 214 (48.9%) | 224 (51.3%) |
| >= 60 Weeks (420 days) | 87 (19.9%) | 104 (23.8%) |
| >= 72 Weeks (504 days) | 7 (1.6%) | 9 (2.1%) |

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.
If the last dose date was completely missing, or only the year was known, or for subjects still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date; in the case where the last study drug end date was nonmissing, it was used to impute the last dose date.
Source: GS-US-366-1160 Week 48, Table 15.11.1.1

### 1.2.2. Postmarketing Data

Odefsey was first approved for the treatment of HIV-1 infection in patients 12 years of age and older in the US on 01 March 2016. As of 31 May 2016, cumulative patient exposure to ODE was estimated to be 1638 patient-years.

## 1.3. Demographic and Other Characteristics of Study Population

### 1.3.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics of subjects in Study GS-US-366-1160 are described in detail in the CSR (GS-US-366-1160 Week 48, Section 8.3.1).

Demographic and baseline characteristics were similar between the 2 treatment groups; no statistically significant differences were observed for any comparison (Table 3). Most subjects were male (87.2%), either white (66.6%) or black (27.2%), and not Hispanic/Latino (81.9%). Median age was 49 years and mean age was 48 years (range: 19 to 76). Median (Q1, Q3) body mass index (BMI) at baseline was 26.0 (23.6, 29.0) kg/m$^2$.

**Table 3. GS-US-366-1160: Demographic and Baseline Characteristics (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) | Total (N = 875) | ODE vs ATR P-Value |
|---|---|---|---|---|
| Age (Years) | | | | |
| N | 438 | 437 | 875 | 0.25 |
| Mean (SD) | 48 (9.8) | 47 (10.5) | 48 (10.1) | |
| Median | 49 | 48 | 49 | |
| Q1, Q3 | 42, 55 | 41, 54 | 41, 54 | |
| Min, Max | 21, 74 | 19, 76 | 19, 76 | |
| Sex at Birth | | | | |
| Male | 373 (85.2%) | 390 (89.2%) | 763 (87.2%) | 0.071 |
| Female | 65 (14.8%) | 47 (10.8%) | 112 (12.8%) | |
| Race | | | | |
| American Indian or Alaska Native | 3 (0.7%) | 2 (0.5%) | 5 (0.6%) | 0.92 |
| Asian | 9 (2.1%) | 8 (1.8%) | 17 (1.9%) | |
| Black | 118 (26.9%) | 120 (27.5%) | 238 (27.2%) | |
| Native Hawaiian or Pacific Islander | 1 (0.2%) | 0 | 1 (0.1%) | |
| White | 291 (66.4%) | 292 (66.8%) | 583 (66.6%) | |
| Not Permitted | 6 (1.4%) | 3 (0.7%) | 9 (1.0%) | |
| Other | 10 (2.3%) | 12 (2.7%) | 22 (2.5%) | |
| Ethnicity | | | | |
| Hispanic or Latino | 79 (18.0%) | 78 (17.8%) | 157 (17.9%) | 0.93 |
| Not Hispanic or Latino | 358 (81.7%) | 359 (82.2%) | 717 (81.9%) | |
| Not Permitted | 1 (0.2%) | 0 | 1 (0.1%) | |
| Baseline Body Mass Index ($kg/m^2$) | | | | |
| N | 438 | 437 | 875 | 0.36 |
| Mean (SD) | 26.9 (5.23) | 26.5 (4.57) | 26.7 (4.92) | |
| Median | 26.1 | 25.9 | 26.0 | |
| Q1, Q3 | 23.4, 29.4 | 23.7, 28.6 | 23.6, 29.0 | |
| Min, Max | 16.5, 51.8 | 17.2, 57.6 | 16.5, 57.6 | |

The denominator for percentage is the number of subjects in the Safety Analysis Set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
For race and ethnicity, observations were the value was "not permitted" were excluded from the CMH test.
Not Permitted = local regulators did not allow collection of race or ethnicity information.
Body mass index ($kg/m^2$) = [Weight (kg)/Height (cm)^2]*10,000.
Source: GS-US-366-1160 Week 48, Table 15.8.3.1

### 1.3.2. Baseline Disease Characteristics

Baseline disease characteristics of subjects in Study GS-US-366-1160 are summarized in Table 4 and described in detail in the CSR (Study GS-US-366-1160 Week 48, Section 8.3.2).

Baseline disease characteristics were similar between the 2 treatment groups. Overall, 98.5% of subjects had baseline HIV-1 RNA < 50 copies/mL. Median (Q1, Q3) baseline CD4 cell count was 667 (505, 852) cells/μL, and the mean (SD) baseline CD4 cell count was 700 (278.4) cells/μL (range: 140 to 1862). The most common HIV risk factor category was homosexual sex (72.1%); 25.4% of subjects reported heterosexual sex as the mode of infection.

Median estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) was similar between the 2 treatment groups. Median (Q1, Q3) baseline $eGFR_{CG}$ was 108.7 (91.5, 132.0) mL/min. Most subjects (92.6%) had no proteinuria by urinalysis (dipstick).

**Table 4. GS-US-366-1160: Baseline Disease Characteristics (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) | Total (N = 875) | ODE vs ATR P-Value |
|---|---|---|---|---|
| HIV-1 RNA Categories (copies/mL) | | | | |
| < 50 | 430 (98.2%) | 432 (98.9%) | 862 (98.5%) | 0.40 |
| ≥ 50 | 8 (1.8%) | 5 (1.1%) | 13 (1.5%) | |
| CD4 Cell Count (/μL) | | | | |
| N | 438 | 437 | 875 | 0.37 |
| Mean (SD) | 711 (292.3) | 688 (263.5) | 700 (278.4) | |
| Median | 673 | 666 | 667 | |
| Q1, Q3 | 507, 887 | 505, 820 | 505, 852 | |
| Min, Max | 140, 1862 | 156, 1727 | 140, 1862 | |
| CD4 Cell Count Categories (/μL) | | | | |
| < 50 | 0 | 0 | 0 | 0.62 |
| ≥ 50 to < 200 | 2 (0.5%) | 5 (1.1%) | 7 (0.8%) | |
| ≥ 200 to < 350 | 41 (9.4%) | 26 (5.9%) | 67 (7.7%) | |
| ≥ 350 to < 500 | 63 (14.4%) | 74 (16.9%) | 137 (15.7%) | |
| ≥ 500 | 332 (75.8%) | 332 (76.0%) | 664 (75.9%) | |
| CD4 Percentage (%) | | | | |
| N | 438 | 437 | 875 | 0.86 |
| Mean (SD) | 36.3 (9.50) | 36.1 (8.75) | 36.2 (9.13) | |
| Median | 36.4 | 36.5 | 36.4 | |
| Q1, Q3 | 30.0, 42.3 | 29.8, 42.1 | 29.9, 42.2 | |
| Min, Max | 7.7, 68.8 | 9.1, 62.1 | 7.7, 68.8 | |
| Mode of Infection (HIV Risk Factors) | | | | |
| Heterosexual Sex | 120 (27.4%) | 102 (23.3%) | 222 (25.4%) | |
| Homosexual Sex | 309 (70.5%) | 322 (73.7%) | 631 (72.1%) | |
| IV Drug Use | 8 (1.8%) | 13 (3.0%) | 21 (2.4%) | |
| Transfusion | 2 (0.5%) | 2 (0.5%) | 4 (0.5%) | |
| Vertical Transmission | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) | |
| Other | 5 (1.1%) | 4 (0.9%) | 9 (1.0%) | |
| Unknown | 13 (3.0%) | 13 (3.0%) | 26 (3.0%) | |

| | ODE (N = 438) | ATR (N = 437) | Total (N = 875) | ODE vs ATR P-Value |
|---|---|---|---|---|
| HIV Disease Status | | | | |
| Asymptomatic | 359 (82.0%) | 377 (86.3%) | 736 (84.1%) | 0.064 |
| Symptomatic HIV Infection | 30 (6.8%) | 26 (5.9%) | 56 (6.4%) | |
| AIDS | 49 (11.2%) | 34 (7.8%) | 83 (9.5%) | |
| Unknown | 0 | 0 | 0 | |
| HBV Surface Antigen Status | | | | |
| Positive | 0 | 0 | 0 | N/A |
| Negative | 438 (100.0%) | 436 (99.8%) | 874 (99.9%) | |
| Missing | 0 | 1 (0.2%) | 1 (0.1%) | |
| HCV Antibody Status | | | | |
| Positive | 31 (7.1%) | 34 (7.8%) | 65 (7.4%) | 0.68 |
| Negative | 407 (92.9%) | 402 (92.0%) | 809 (92.5%) | |
| Missing | 0 | 1 (0.2%) | 1 (0.1%) | |
| Estimated Glomerular Filtration Rate by Cockcroft-Gault (mL/min) | | | | |
| N | 438 | 437 | 875 | 0.63 |
| Mean (SD) | 114.0 (31.88) | 113.2 (32.28) | 113.6 (32.06) | |
| Median | 110.4 | 107.6 | 108.7 | |
| Q1, Q3 | 91.4, 132.0 | 91.6, 132.7 | 91.5, 132.0 | |
| Min, Max | 54.0, 239.0 | 50.2, 259.9 | 50.2, 259.9 | |
| Proteinuria by Urinalysis (dipstick) | | | | |
| Grade 0 | 410 (93.6%) | 400 (91.5%) | 810 (92.6%) | 0.33 |
| Grade 1 | 26 (5.9%) | 36 (8.2%) | 62 (7.1%) | |
| Grade 2 | 2 (0.5%) | 1 (0.2%) | 3 (0.3%) | |
| Grade 3 | 0 | 0 | 0 | |

N/A = not applicable
The denominator for percentage is the number of subjects in the Safety Analysis Set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Percentages may add to more than 100% for the HIV risk factor category and enrollment survey as a subject may provide more than 1 response.
For urine protein by dipstick, the highest grade is up to Grade 3.
Source: GS-US-366-1160 Week 48, Table 15.8.3.2

# 2. ADVERSE EVENTS

## 2.1. Analysis of Adverse Events

Adverse events for subjects in Study GS-US-366-1160 are described in detail in the CSR (GS-US-366-1160 Week 48, Section 11.2).

A higher percentage of subjects in the ODE group than the ATR group had any AE reported (ODE 80.1%, 351 of 438 subjects; ATR 73.9%, 323 of 437 subjects). Similar percentages of subjects in each group had a Grade 2, 3, or 4 AE (ODE 35.4%, 155 subjects; ATR 33.6%, 147 subjects), or an SAE (ODE 5.5%, 24 subjects; ATR 5.7%, 25 subjects) (Table 5).

Similar percentages of subjects in each group had a Grade 3 or 4 AE (ODE 6.2%, 27 subjects; ATR 5.7%, 25 subjects). No subject in the ODE group and 2 subjects in the ATR group (0.5%) had a study drug-related Grade 3 or 4 AE. No subject in the ODE group and 1 subject in the ATR group (0.2%) had a study drug-related SAE.

Subjects who switched to ODE had a slightly higher incidence of any AE considered by the investigator as related to study drug (ODE 12.8%, 56 subjects; ATR 10.3%, 45 subjects).

Adverse events that led to study drug discontinuation were uncommon in both groups (ODE 2.5%, 11 subjects; ATR 1.8%, 8 subjects). One subject in the ODE group (0.2%) died during the study as a result of a methamphetamine/cocaine drug overdose. No death occurred in the ATR group.

**Table 5. GS-US-366-1160: Overall Summary of Adverse Events (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 351 (80.1%) | 323 (73.9%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 155 (35.4%) | 147 (33.6%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 27 (6.2%) | 25 (5.7%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 56 (12.8%) | 45 (10.3%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 11 (2.5%) | 19 (4.3%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 0 | 2 (0.5%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 24 (5.5%) | 25 (5.7%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 0 | 1 (0.2%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 11 (2.5%) | 8 (1.8%) |
| Subjects who had Treatment-Emergent Death | 1 (0.2%) | 0 |

Adverse events were coded using MedDRA version 19.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Treatment-emergent death refers to a death which occurred between the first dose date and the last dose date plus 30 days (inclusive).
Source: GS-US-366-1160 Week 48, Table 15.11.2.1.1

### 2.1.1. Common Adverse Events

Adverse events for subjects in Study GS-US-366-1160 are described in detail in the CSR (Study GS-US-366-1160 Week 48, Section 11.2).

The following were the most commonly reported AEs that occurred in ≥ 5% of subjects in either treatment group (Table 6):

- ODE: upper respiratory tract infection (10.0%, 44 of 438 subjects), nasopharyngitis (7.8%, 34 subjects), cough (5.9%, 26 subjects), and headache (5.5%, 24 subjects)
- ATR: upper respiratory tract infection (9.6%, 42 of 437 subjects), diarrhea (7.3%, 32 subjects), and arthralgia (5.5%, 24 subjects)

Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs.

No AE by preferred term (PT) was reported with a difference in percentages of ≥ 5% between groups.

**Table 6. GS-US-366-1160: Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) |
|---|---|---|
| Number of Subjects Experiencing Any Treatment-Emergent Adverse Event | 351 (80.1%) | 323 (73.9%) |
| Gastrointestinal disorders | 111 (25.3%) | 100 (22.9%) |
| Diarrhea | 21 (4.8%) | 32 (7.3%) |
| Infections and infestations | 179 (40.9%) | 174 (39.8%) |
| Upper respiratory tract infection | 44 (10.0%) | 42 (9.6%) |
| Nasopharyngitis | 34 (7.8%) | 19 (4.3%) |
| Musculoskeletal and connective tissue disorders | 81 (18.5%) | 88 (20.1%) |
| Arthralgia | 20 (4.6%) | 24 (5.5%) |
| Nervous system disorders | 65 (14.8%) | 47 (10.8%) |
| Headache | 24 (5.5%) | 17 (3.9%) |
| Respiratory, thoracic and mediastinal disorders | 63 (14.4%) | 47 (10.8%) |
| Cough | 26 (5.9%) | 15 (3.4%) |

Adverse events were coded using MedDRA version 19.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
System organ class (SOC) and high level term (within each SOC) were presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-366-1160 Week 48, Table 15.11.2.1.2

### Adverse Events by Severity

Most AEs reported in either treatment group of Study GS-US-366-1160 were Grade 1 or 2 in severity (Table 5). Similar percentages of subjects in each group had a Grade 3 or 4 AE (ODE 6.2%, 27 subjects; ATR 5.7%, 25 subjects); most of these subjects had no Grade 4 events, but rather had AEs that were Grade 3 as worst severity (ODE 24 of 27 subjects; ATR 21 of 25 subjects). No pattern was observed in the type of Grade 3 or 4 events. Grade 4 events occurred in approximately 1% of subjects in both groups.

No Grade 3 or 4 AEs by PT were reported for ≥ 1% of subjects in either group.

### Adverse Events Considered Related to Study Drug

A slightly higher percentage of subjects in the ODE group than in the ATR group had any AE considered by the investigator as related to study drug in Study GS-US-366-1160 (ODE 12.8%, 56 subjects; ATR 10.3%, 45 subjects).

The most common AEs considered related to study drug by the investigator, reported for ≥ 1% of subjects in either group were as follows:

- ODE: headache (1.6%, 7 subjects), flatulence (1.4%, 6 subjects), and insomnia (1.1%, 5 subjects)
- ATR: diarrhea (2.5%, 11 subjects) and abnormal dreams (1.1%, 5 subjects)

### 2.1.2. Deaths

One subject in the ODE group died during Study GS-US-366-1160 as a result of a methamphetamine/cocaine drug overdose. No death occurred in the ATR group.

### 2.1.3. Other Serious Adverse Events

Similar percentages of subjects in each group had an SAE in Study GS-US-366-1160 (ODE 5.5%, 24 subjects; ATR 5.7%, 25 subjects) (GS-US-366-1160 Week 48, Section 11.5).

The only SAEs occurring in > 1 subject in either treatment group were coronary artery disease, myocardial infarction, and cholelithiasis, each reported in 2 subjects (0.5%) in the ODE group, and pneumonia, reported in 2 subjects (0.5%) in the ATR group.

Of the 4 SAEs associated with coronary artery events in the ODE group, 2 had identified alternative causes (cocaine use; diabetes miletus and preexisting peripheral artery disease). For the other 2 events, 1 male subject was 6[redacted] years old with elevated total cholesterol at baseline, and the other had normal baseline lipids.

No SAE in the ODE group was considered related to study drug by the investigator. One SAE in the ATR group (atrial fibrillation) was considered related to study drug by the investigator.

### 2.1.4. Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section.

Adverse events that led to study drug discontinuation in Study GS-US-366-1160 were low in both groups (ODE 2.5%, 11 subjects; ATR 1.8%, 8 subjects). Most AEs leading to discontinuation of study drugs were nonserious. The only AEs leading to study drug discontinuation reported for > 1 subject in either treatment group were fatigue and cough, each reported in 2 subjects (0.5%) in the ODE group.

Twelve subjects had study drug-related AEs leading to study drug discontinuation (ODE 1.1%, 5 subjects; ATR 1.6%, 7 subjects). No study drug-related AE that led to study drug discontinuation was reported for more than 1 subject in each group.

## 2.1.5. Analysis of Adverse Events by Organ System or Syndrome

### 2.1.5.1. Bone Safety

Bone safety for subjects in Study GS-US-366-1160 is described in detail in the CSR (Study GS-US-366-1160 Week 48, Section 11.2.4.1).

#### 2.1.5.1.1. Fracture Events

The percentages of subjects with fracture events were low in both treatment groups in Study GS-US-366-1160 (ODE 1.8%, 8 subjects; ATR 0.9%, 4 subjects; p = 0.38). In the ODE group, 3 of the fracture events were reported as SAEs: multiple fractures, pathological fracture, and fibula fracture. All the other fracture events were nonserious.

All reported fracture events were considered by the investigator as unrelated to the study drug. The SAE of multiple fractures (together with a concomitant SAE of road traffic accident) in a subject in the ODE group resulted in permanent discontinuation of study drug; none of the other fracture events resulted in study drug discontinuation. Most fracture events were the result of trauma with the exception of 1 (subject had multiple pathologic rib fractures with causality of prostate cancer with bone metastasis).

#### 2.1.5.1.2. Percentage Change from Baseline in Hip and Spine BMD

There were increases from baseline in hip and spine BMD in the ODE group compared with minimal changes from baseline in both parameters in the ATR group in Study GS-US-366-1160 ($p < 0.001$ for the differences between groups at Weeks 24 and 48) (Table 7).

Mean (SD) percentage changes from baseline in hip and spine BMD at Week 48 (observed data) were as follows:

- Hip
  - ODE: 1.279% (2.3800%)
  - ATR: –0.134% (2.4930%)
- Spine
  - ODE: 1.645% (3.3198%)
  - ATR: –0.045% (2.9087%)

**Table 7. GS-US-366-1160: Percentage Change from Baseline in Hip and Spine BMD by Visit (Observed Data; Hip or Spine DXA Analysis Set)**

| | Statistic | ODE | ATR | ODE vs ATR | |
|---|---|---|---|---|---|
| | | | | P-Value | Difference in LSM (95% CI) |
| **Hip BMD** | | | | | |
| Baseline ($g/cm^2$) | N | 388 | 399 | 0.82 | 0.002 (−0.018, 0.023) |
| | Mean (SD) | 0.981 (0.1483) | 0.979 (0.1417) | | |
| % Change at Week 24 | N | 369 | 382 | < 0.001 | 0.911 (0.611, 1.212) |
| | Mean (SD) | 0.902 (2.1863) | −0.009 (2.0070) | | |
| % Change at Week 48 | N | 347 | 367 | < 0.001 | 1.413 (1.054, 1.771) |
| | Mean (SD) | 1.279 (2.3800) | −0.134 (2.4930) | | |
| **Spine BMD** | | | | | |
| Baseline ($g/cm^2$) | N | 394 | 400 | 0.89 | −0.002 (−0.027, 0.023) |
| | Mean (SD) | 1.112 (0.1831) | 1.114 (0.1765) | | |
| % Change at Week 24 | N | 373 | 382 | < 0.001 | 1.119 (0.709, 1.530) |
| | Mean (SD) | 1.226 (3.0353) | 0.106 (2.7063) | | |
| % Change at Week 48 | N | 351 | 369 | < 0.001 | 1.690 (1.234, 2.146) |
| | Mean (SD) | 1.645 (3.3198) | −0.045 (2.9087) | | |

% Change = Change from baseline at a postbaseline visit / baseline * 100%
P-Values, difference in LSMs, and its 95% CI were from the ANOVA model including treatment as a fixed effect.
Source: GS-US-366-1160 Week 48, Tables 15.11.2.4.1.2 and 15.11.2.4.1.4

### Categorical Distribution of Percentage Change from Baseline in BMD

Differences between the 2 treatment groups in the categorical distribution of percentage change from baseline in hip, spine, and femoral neck BMD were statistically significant at Weeks 24 and 48 in Study GS-US-366-1160 ($p < 0.001$). There was evidence for an improvement in BMD after switching to ODE.

The percentages of subjects with ≥ 3% increases from baseline in hip and spine BMD at Week 48 were higher in the ODE group than in the ATR group, as follows (Table 8):

- Hip
  - ODE: 18.7%
  - ATR: 6.3%
- Spine
  - ODE: 29.1%
  - ATR: 12.7%

The percentages of subjects with ≥ 3% decreases from baseline in hip and spine BMD at Week 48 were lower in the ODE group than in the ATR group, as follows:

- Hip
  - ODE: 2.3%
  - ATR: 10.1%
- Spine
  - ODE: 6.6%
  - ATR: 13.8%

The percentages of subjects with ≥ 7% decreases from baseline in femoral neck BMD or ≥ 5% decreases from baseline in spine BMD at Week 48 were also lower in the ODE group (1.4% and 2.3%, respectively) than in the ATR group (3.3% and 4.9%, respectively) ($p < 0.001$ for the difference between groups at Week 48).

**Table 8. GS-US-366-1160: Percentage Change from Baseline in Hip and Spine BMD by Visit (Observed Data; Hip or Spine DXA Analysis Set)**

| | Visit | ODE n/N (%) | ATR n/N (%) |
|---|---|---|---|
| **Hip BMD** | | | |
| ≥ 3% Decrease | Week 24 | 8/369 (2.2%) | 16/382 (4.2%) |
| | Week 48 | 8/347 (2.3%) | 37/367 (10.1%) |
| No Decrease (≥ 0% Change) | Week 24 | 245/369 (66.4%) | 183/382 (47.9%) |
| | Week 48 | 248/347 (71.5%) | 178/367 (48.5%) |
| ≥ 3% Increase | Week 24 | 46/369 (12.5%) | 24/382 (6.3%) |
| | Week 48 | 65/347 (18.7%) | 23/367 (6.3%) |
| **Spine BMD** | | | |
| ≥ 3% Decrease | Week 24 | 26/373 (7.0%) | 42/382 (11.0%) |
| | Week 48 | 23/351 (6.6%) | 51/369 (13.8%) |
| No Decrease (≥ 0% Change) | Week 24 | 251/373 (67.3%) | 188/382 (49.2%) |
| | Week 48 | 251/351 (71.5%) | 182/369 (49.3%) |
| ≥ 3% Increase | Week 24 | 98/373 (26.3%) | 54/382 (14.1%) |
| | Week 48 | 102/351 (29.1%) | 47/369 (12.7%) |

Source: GS-US-366-1160 Week 48, Tables 15.11.2.4.1.6 and 15.11.2.4.1.7

#### 2.1.5.1.3. Bone Laboratory Parameters

Serum levels of PTH decreased from baseline in the ODE group and increased from baseline in the ATR group at Week 48 in Study GS-US-366-1160 ($p < 0.001$ for the differences between groups). Serum levels of CTx increased from baseline in both the ODE and ATR groups at Week 48, with a greater increase in the ODE group than in the ATR group ($p = 0.007$ for the difference between groups). Serum levels of P1NP decreased from baseline in both the ODE and ATR groups at Week 48, with a greater decrease from baseline in the ODE group than in the ATR group ($p < 0.001$ for the difference between groups). Median (Q1, Q3) percentage changes from baseline in PTH, CTx, and P1NP at Week 48 were as follows:

- PTH
  - ODE: −11.3% (−30.2%, 11.5%)
  - ATR: 8.6% (−13.8%, 33.4%)
- CTx
  - ODE: 12.0% (−3.4%, 29.0%)
  - ATR: 7.1% (−6.1%, 22.0%)
- P1NP
  - ODE: −25.12% (−37.19%, −10.37%)
  - ATR: −5.63% (−18.22%, 10.59%)

### 2.1.5.2. Renal Safety

Renal safety for subjects in Study GS-US-366-1160 is described in detail in the CSR (Study GS-US-366-1160 Week 48, Section 11.2.4.2).

#### 2.1.5.2.1. Renal Events

No subject had a renal SAE in Study GS-US-366-1160.

One subject in the ODE group discontinued study drug due to a renal AE (decreased glomerular filtration rate). The investigator assessed the AE as related to study drug. No subject in the ATR group discontinued study drug due to a renal AE.

There were no cases of proximal renal tubulopathy (including Fanconi syndrome) reported during the study.

#### 2.1.5.2.2. Renal Laboratory Parameters

##### 2.1.5.2.2.1. Serum Creatinine

An increase in serum creatinine from baseline in the ODE group was observed at Week 4 and was stable from Week 12 through Week 48 with minimal or no change from baseline in the ATR group in Study GS-US-366-1160. The difference between groups in the change from baseline in serum creatinine was statistically significant at all time points from Week 4 through Week 48 ($p < 0.001$ for the difference between groups at all time points from Week 4 through Week 48) (Table 9). The increase in creatinine in the ODE group is consistent with the known effects of RPV on tubular secretion of creatinine and does not represent a true change in renal function.

**Table 9. GS-US-366-1160: Change from Baseline in Serum Creatinine (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) | P-Value |
|---|---|---|---|
| Baseline (mg/dL) | | | |
| N | 438 | 437 | 0.38 |
| Mean (SD) | 0.93 (0.156) | 0.94 (0.166) | |
| Median | 0.93 | 0.93 | |
| Q1, Q3 | 0.82, 1.03 | 0.82, 1.05 | |
| Change at Week 48 (mg/dL) | | | |
| N | 394 | 402 | < 0.001 |
| Mean (SD) | 0.06 (0.102) | 0.01 (0.105) | |
| Median | 0.07 | 0.00 | |
| Q1, Q3 | 0.00, 0.13 | −0.06, 0.06 | |

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-366-1160 Week 48, Table 15.11.2.4.2.1

##### 2.1.5.2.2.2. Estimated Glomerular Filtration Rate

A decrease in $eGFR_{CG}$ from baseline was observed in the ODE group at Week 4 and was stable from Week 12 through Week 48, compared with minimal changes from baseline in the ATR group in Study GS-US-366-1160. The difference between groups in the change from baseline in $eGFR_{CG}$ was statistically significant at all time points from Week 4 through Week 48 ($p < 0.001$ at all time points from Week 4 through Week 48) (Table 10). The decrease in $eGFR_{CG}$ in the ODE group is consistent with the known effects of RPV on tubular secretion of creatinine, has no effect on actual glomerular filtration, does not represent a true change in renal function, and is not considered clinically relevant.

**Table 10. GS-US-366-1160: Change from Baseline in $eGFR_{CG}$ (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) | P-Value |
|---|---|---|---|
| Baseline (mL/min) | | | |
| N | 438 | 437 | 0.63 |
| Mean (SD) | 114.0 (31.88) | 113.2 (32.28) | |
| Median | 110.4 | 107.6 | |
| Q1, Q3 | 91.4, 132.0 | 91.6, 132.7 | |
| Change at Week 48 (mL/min) | | | |
| N | 394 | 402 | < 0.001 |
| Mean (SD) | −4.3 (13.73) | −0.5 (13.99) | |
| Median | −4.1 | −0.6 | |
| Q1, Q3 | −12.7, 4.6 | −7.8, 6.7 | |

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-366-1160 Week 48, Table 15.11.2.4.2.2

2.1.5.2.2.3. Proteinuria by Urinalysis (Dipstick)

The majority of subjects in both treatment groups in Study GS-US-366-1160 had no proteinuria (Grade 0 by dipstick) at baseline and through Week 48. The percentage of subjects with improvement from baseline (toxicity grade decreased at least 1 grade from baseline) in proteinuria toxicity grade at Week 48 was higher in the ODE group than in the ATR group, as follows:

- ODE: 80.0% (20 of 25 subjects)
- ATR: 65.6% (21 of 32 subjects)

The percentage of subjects with proteinuria grade worsening from baseline at Week 48 was similar between groups as follows:

- ODE: 4.6% (18 of 391 subjects)
- ATR: 5.2% (21 of 401 subjects)

2.1.5.2.2.4. Proteinuria by Quantitative Assessment

Decreases from baseline in median UPCR and UACR were observed in the ODE group through Week 48 compared with mostly increases from baseline in the ATR group in Study GS-US-366-1160 ($p < 0.001$ for the differences in percentage change from baseline between groups at Week 48) (Table 11).

**Table 11. GS-US-366-1160: Change from Baseline in UPCR and UACR (Safety Analysis Set)**

| | ODE (N = 438) | | | ATR (N = 437) | | | |
|---|---|---|---|---|---|---|---|
| | N | Median (Q1, Q3) | Median (Q1, Q3) % Change from Baseline | N | Median (Q1, Q3) | Median (Q1, Q3) % Change from Baseline | P-Value |
| UPCR (mg/g) at Baseline | 438 | 63.3 (40.8, 105.4) | — | 437 | 62.2 (40.7, 108.7) | — | 0.91 |
| At Week 48 | 391 | 45.3 (30.6, 78.6) | −30.0% (−54.4%, 18.9%) | 401 | 60.9 (38.6, 108.7) | −2.0% (−35.6%, 42.0%) | < 0.001 |
| UACR (mg/g) at Baseline | 438 | 6.9 (4.2, 13.6) | — | 437 | 6.4 (4.3, 11.8) | — | 0.40 |
| At Week 48 | 392 | 5.6 (3.8, 10.3) | −13.5% (−47.5%, 25.3%) | 400 | 7.0 (4.7, 13.9) | 12.2% (−20.0%, 55.6%) | < 0.001 |

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-366-1160 Week 48, Tables 15.11.2.4.2.4 and 15.11.2.4.2.5

Most subjects in both treatment groups had no clinically significant proteinuria (UPCR > 200 mg/g) or albuminuria (UACR ≥ 30 mg/g) at baseline and through Week 48.

2.1.5.2.2.5. Proximal Tubular Proteinuria Assessments

Decreases from baseline in median urine RBP to creatinine ratio and urine β2M to creatinine ratio at Weeks 24 and 48 were observed in the ODE group compared with increases, for subjects who remained on ATR in Study GS-US-366-1160 ($p < 0.001$ for the differences in percentage change from baseline between groups at Week 48) (Table 12).

**Table 12. GS-US-366-1160: Changes from Baseline in Urine RBP to Creatinine Ratio and Urine β2M to Creatinine Ratio (Safety Analysis Set)**

| | ODE (N = 438) | | | | ATR (N = 437) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median (Q1, Q3) | N[a] | Median (Q1, Q3) % Change from Baseline | N | Median (Q1, Q3) | N[a] | Median (Q1, Q3) % Change from Baseline |
| Urine RBP to Creatinine Ratio (µg/g) at Baseline | 433 | 115.8 (75.0, 254.4) | — | — | 434 | 131.8 (82.7, 265.7) | — | — |
| At Week 48 | 400 | 89.7 (61.9, 151.8) | 396 | −27.6% (−58.8%, 4.2%) | 406 | 165.6 (100.6, 358.6) | 403 | 29.1% (−13.4%, 96.8%) |
| Urine β2M to Creatinine Ratio (µg/g) at Baseline | 428 | 130.1 (69.0, 498.6) | — | — | 428 | 153.6 (78.8, 480.8) | — | — |
| At Week 48 | 398 | 82.4 (57.8, 146.3) | 389 | −41.0% (−74.5%, 0.8%) | 406 | 185.9 (80.5, 797.5) | 398 | 17.1% (−34.1%, 135.7%) |

a Number of subjects with nonmissing values at baseline and the specified study visit.
Source: GS-US-366-1160 Week 48, Tables 15.11.2.4.2.8 and 15.11.2.4.2.9

#### 2.1.5.3. HIV Symptoms Index Score

The HIV symptoms index questionnaire was completed by each subject at prespecified timepoints in Study GS-US-366-1160; results are summarized below and described in detail in the CSR (Study GS-US-366-1160 Week 48, Section 11.2.4.3).

The total HIV symptoms index score in Study GS-US-366-1160, counting the number of bothersome symptoms from 20 HIV-related symptoms, were balanced between treatment groups at baseline (mean [SD] baseline values: ODE 4 [4.3]; ATR 4 [4.2]). The low baseline scores in both groups indicated that subjects did not find their HIV symptoms bothersome at baseline, which was not unexpected in a population of subjects on a stable ATR regimen prior to study entry. At Week 48, there was no change in the mean total HIV symptoms index score in the ODE group compared with a decrease (improvement) in the ATR group (mean [SD] change from baseline at Week 48: ODE 0 [3.4], ATR –1 [3.4]; difference in least-squares mean: 1, 95% CI: 0 to 1; p = 0.009). There were minimal changes in the number of bothersome HIV symptoms in both groups over the 48-week period, and the difference is not considered clinically relevant.

## 2.2. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures, if applicable, are provided in the relevant CSRs.

# 3. CLINICAL LABORATORY EVALUATIONS

All laboratory abnormalities discussed in the following sections were treatment-emergent and are referred to as laboratory abnormalities.

## 3.1. Laboratory Abnormalities

Laboratory abnormalities for subjects in Study GS-US-366-1160 are described in detail in the CSR (GS-US-366-1160 Week 48, Section 11.7.3).

Most subjects had at least 1 laboratory abnormality during the study (ODE 80.1%, 350 of 437 subjects; ATR 77.0%, 334 of 434 subjects); most of the reported abnormalities were Grade 1 or Grade 2.

The incidence of laboratory abnormalities of any grade was similar between treatment groups for most chemistry, hematology, and urinalysis parameters. Overall, similar percentages of subjects in each group had a Grade 3 or 4 laboratory abnormality (ODE 9.8%, 43 subjects; ATR 9.0%, 39 subjects) (Table 13).

**Table 13. GS-US-366-1160: Grade 3 and 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) |
|---|---|---|
| Maximum Post-Baseline Toxicity Grade | 437 | 434 |
| Grade 3 | 35 (8.0%) | 36 (8.3%) |
| Grade 4 | 8 (1.8%) | 3 (0.7%) |
| Grade 3 or 4 | 43 (9.8%) | 39 (9.0%) |
| Chemistry | | |
| Creatine Kinase | 437 | 434 |
| Grade 3 | 6 (1.4%) | 7 (1.6%) |
| Grade 4 | 4 (0.9%) | 0 |
| Grade 3 or 4 | 10 (2.3%) | 7 (1.6%) |
| Serum Glucose (Fasting, Hyperglycemia) | 428 | 422 |
| Grade 3 | 6 (1.4%) | 0 |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 6 (1.4%) | 0 |

| | ODE (N = 438) | ATR (N = 437) |
|---|---|---|
| Serum Glucose (Nonfasting, Hyperglycemia) | 435 | 433 |
| Grade 3 | 7 (1.6%) | 3 (0.7%) |
| Grade 4 | 2 (0.5%) | 0 |
| Grade 3 or 4 | 9 (2.1%) | 3 (0.7%) |
| Total Cholesterol (Fasting, Hypercholesterolemia) | 416 | 418 |
| Grade 3 | 2 (0.5%) | 4 (1.0%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 2 (0.5%) | 4 (1.0%) |
| LDL (Fasting) | 416 | 418 |
| Grade 3 | 8 (1.9%) | 11 (2.6%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 8 (1.9%) | 11 (2.6%) |
| Urinalysis | | |
| Urine Glucose (Glycosuria) | 437 | 434 |
| Grade 3 | 10 (2.3%) | 4 (0.9%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 10 (2.3%) | 4 (0.9%) |
| Urine RBC (Hematuria, Quantitative) | 437 | 434 |
| Grade 3 | 5 (1.1%) | 5 (1.2%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 5 (1.1%) | 5 (1.2%) |

The denominator for percentage is the number of subjects in the safety analysis set with at least 1 postbaseline value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
For urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
For nonfasting serum glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting serum glucose test was not done for all subjects at baseline.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Source: GS-US-366-1160 Week 48, Table 15.11.6.4.2

## 3.2. Liver-Related Laboratory Parameters

In the assessment of liver enzyme elevations in relation to normal ranges in Study GS-US-366-1160, no subject had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN), total bilirubin > 2 × ULN, and alkaline phosphatase < 2 × ULN. No Hy's Law cases were identified.

### 3.3. Metabolic Laboratory Parameters

Metabolic laboratory parameters for subjects in Study GS-US-366-1160 are described in detail in the CSR (GS-US-366-1160 Week 48, Section 11.7.5).

There were decreases from baseline in fasting values of total cholesterol and high-density lipoprotein (HDL) cholesterol in the ODE group, while these parameters had little change or slightly decreased in the ATR group at both Week 24 and Week 48 ($p \leq 0.001$ for the differences between groups in change from baseline at Weeks 24 and 48; Table 14). There were no clinically significant changes from baseline in the fasting values for the total cholesterol to HDL ratio, triglycerides, or glucose for either treatment group. Findings were similar when the analysis excluded subjects who were taking lipid-modifying medications (GS-US-366-1160 Week 48, Tables 15.11.6.3.9 to 15.11.6.3.13).

**Table 14. GS-US-366-1160: Changes from Baseline in Fasting Metabolic Assessments at Week 48 (Safety Analysis Set)**

| | ODE (N = 438) | | ATR (N = 437) | |
|---|---|---|---|---|
| **Metabolic Assessment** | **N** | **Mean (SD)** | **N** | **Mean (SD)** |
| Fasting Total Cholesterol (mg/dL) | | | | |
| Baseline | 429 | 192 (31.7) | 432 | 192 (35.8) |
| Change at Week 48 | 384 | −8 (28.6) | 396 | −3 (27.1) |
| Fasting Direct LDL Cholesterol (mg/dL) | | | | |
| Baseline | 429 | 117 (28.1) | 432 | 119 (31.1) |
| Change at Week 48 | 384 | −2 (24.3) | 396 | −1 (22.2) |
| Fasting HDL Cholesterol (mg/dL) | | | | |
| Baseline | 429 | 55 (17.4) | 432 | 55 (16.9) |
| Change at Week 48 | 384 | −4 (9.9) | 396 | −1 (10.0) |
| Fasting Total Cholesterol to HDL Ratio | | | | |
| Baseline | 429 | 3.8 (1.28) | 432 | 3.8 (1.83) |
| Change at Week 48 | 384 | 0.2 (2.14) | 396 | 0.0 (1.40) |
| Fasting Triglycerides (mg/dL) | | | | |
| Baseline | 429 | 146 (113.6) | 432 | 140 (93.4) |
| Change at Week 48 | 384 | −12 (82.3) | 396 | 2 (76.0) |
| Fasting Glucose (mg/dL) | | | | |
| Baseline | 430 | 100 (22.4) | 430 | 99 (18.4) |
| Change at Week 48 | 387 | −2 (23.3) | 396 | −1 (13.8) |

Only laboratory measurements under fasting status were summarized.
Baseline value was the last available value collected on or prior to first dose date of study drug.
Source: GS-US-366-1216 Week 48, Tables 15.11.6.3.1 to 15.11.6.3.6

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Detailed information on vital signs, physical findings, and other observations related to safety may be found in the CSR for this study (GS-US-366-1160 Week 48, Section 11.8). Results of safety ECG assessments are described in this section for Study GS-US-366-1160, along with changes from baseline in body weight.

## 4.1. Electrocardiogram

Among subjects who had ECG results available at Baseline and Week 24 or 48 in Study GS-US-366-1160, clinically significant ECG findings were reported at Week 24 for 2 of 425 subjects (0.5%) in the ODE group and 1 of 417 subjects (0.2%) in the ATR group, and at Week 48 for 4 of 400 subjects (1.0%) in the ODE group and 2 of 406 subjects (0.5%) in the ATR group.

Adverse events related to ECGs were reported in 4 subjects in the ODE group and for 1 in the ATR group. These AEs were nonserious, Grade 1 or 2 in severity, and did not result in study drug discontinuation. Two of these AEs, 1 in each study group (ODE: electrocardiogram ST segment elevation; ATR: electrocardiogram QT prolonged), were considered related to study drug by the investigator.

## 4.2. Body Weight

There were no clinically relevant changes from baseline or between treatment groups in median values for body weight in either treatment group in Study GS-US-366-1160.

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

For subjects who switched from ATR (Study GS-US-366-1160), AE incidence was analyzed by sex, age, and race. The results of these analyses are described in the CSR (GS-US-366-1160 Week 48, Section 11.3).

The AEs associated with ODE in Study GS-US-366-1160 were lower in males than females, comparable among subjects < 50 years and those ≥ 50 years, and lower in black than nonblack subjects. Overall, the AE profile for ODE was similar across the subgroups of sex, age, and race, acknowledging the small numbers of subjects in some subgroups, as described below.

### 5.1.1. Sex

The percentages of subjects experiencing any AE in Study GS-US-366-1160 were lower in males than females in both treatment groups (ODE: male 79.1%, 295 of 373 subjects; female 86.2%, 56 of 65 subjects; ATR: male 72.8%, 284 of 390; female 83.0%, 39 of 47 subjects).

### 5.1.2. Age

The percentages of subjects with any AE in Study GS-US-366-1160 were comparable in subjects < 50 and ≥ 50 years in both treatment groups (ODE: < 50 years 79.4%, 185 of 233 subjects; ≥ 50 years 81.0%, 166 of 205 subjects; ATR: < 50 years 74.9%, 179 of 239; ≥ 50 years 72.7%, 144 of 198 subjects).

### 5.1.3. Race

The percentages of subjects experiencing any AE in Study GS-US-366-1160 were lower among black than nonblack in the ODE group (black 75.4%, 89 of 118 subjects; nonblack 82.2%, 258 of 314 subjects) but comparable in black and nonblack subjects in the ATR group (black 71.1%, 86 of 120 subjects; nonblack 74.5%, 234 of 314 subjects).

## 5.2. Extrinsic Factors

For subjects who switched from ATR (Study GS-US-366-1160), AE incidence was analyzed by region. The results of this analysis are described in the CSR (GS-US-366-1160 Week 48, Section 11.3). The AEs associated with ODE in Study GS-US-366-1160 were comparable in subjects from the US and those from Ex-US regions. Overall, the AE profile for ODE was similar across the subgroup of region, as described below.

### 5.2.1. Region

The percentages of subjects experiencing any AE in Study GS-US-366-1160 were comparable in subjects from the US and Ex-US regions in the ODE group (US 79.8%, 280 of 351 subjects; Ex-US 81.6%, 71 of 87 subjects) but lower in subjects from the US than those from Ex-US regions in the ATR group (US 72.8%, 251 of 345 subjects; Ex-US 78.3%, 72 of 92 subjects).

## 5.3. Drug Interactions

No new information is presented.

## 5.4. Use in Pregnancy and Lactation

A confirmed pregnancy was reported in 1 subject in the ATR group on Day 274 in Study GS-US-366-1160, and study drug was discontinued (GS-US-366-1160 Week 48, Listing 16.2.8.6). The estimated date of delivery is [redacted] (Day 546). No updates have been reported.

## 5.5. Overdose

No new safety issues have been identified regarding overdose since the original marketing application.

## 5.6. Drug Abuse

No safety issues concerning the abuse or misuse of ODE tablets are anticipated from the available data.

## 5.7. Withdrawal and Rebound

No new information is presented.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No new information is presented.

# 6. POSTMARKETING DATA

Postmarketing safety data for ODE and its individual components are carefully evaluated on an ongoing basis for any new safety issues and the labeling changes are submitted to regulatory authorities when new adverse reactions are identified. There have been no newly identified adverse reactions for ODE based on the postmarketing data available to date.

# 7. REFERENCES

No references are included.

# 8. APPENDIX

No appendices are included.

**SECTION 2.7**
**CLINICAL SUMMARY**

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## SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)
# SUBMISSION REF. NO. : ODE-16-080
# (STUDY GS-US-366-1216)

Gilead Sciences

17 October 2016

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| β2M | beta-2-microglobulin |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| BMD | bone mineral density |
| BMI | body mass index |
| CD4 | cluster determinant 4 |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CPA | emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®/Eviplera®) |
| CSR | clinical study report |
| CTx | C-terminal telopeptide |
| DDI | drug-drug interaction |
| DXA | dual-energy x-ray absorptiometry |
| ECG | electrocardiogram |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| FTC | emtricitabine (Emtriva®) |
| Gilead | Gilead Sciences |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| IV | intravenous |
| LDL | low-density lipoprotein |
| LSM | least-squares mean |
| m | Module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | not applicable |
| N or n | number of subjects in a population (N) or subset (n) |
| ODE | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| P1NP | procollagen type 1 N-terminal propeptide |
| PT | preferred term |
| PTH | parathyroid hormone |
| Q1, Q3 | first quartile, third quartile |
| RBC | red blood cell |
| RBP | retinol binding protein |

| | |
|---|---|
| RNA | ribonucleic acid |
| RPV | rilpivirine |
| SAE | serious adverse event |
| SD | standard deviation |
| SOC | system organ class |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| UACR | urine albumin to creatinine ratio |
| ULN | upper limit of normal |
| UPCR | urine protein to creatinine ratio |
| US | United States |
| vs | versus |

# 1. EXPOSURE TO THE DRUG

Odefsey® (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]) is an oral, once-daily, fixed-dose combination that provides an effective and complete option for the long-term treatment of patients infected with HIV-1. Odefsey contains the nucleoside reverse transcriptase inhibitor FTC, the non-nucleoside reverse transcriptase inhibitor RPV, and the nucleotide reverse transcriptase inhibitor TAF. Odefsey was approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States (US) on 01 March 2016 and in the European Union on 21 June 2016.

Data in this document support updates to the product information for ODE. See also Module 2.7.3 Summary of Clinical Efficacy for Study GS-US-366-1160 which is also provided in this grouped application.

## 1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

### 1.1.1. Primary Safety Population for Odefsey

This document provides additional safety data for HIV-infected, virologically suppressed adults who switched treatment to ODE from the following (Table 1):

- FTC/RPV/tenofovir disoproxil fumarate (TDF) (Complera®/Eviplera® [CPA]) (Study GS-US-366-1216): results through 48 weeks of treatment (primary endpoint at 48 weeks)

Data were not pooled across studies GS-US-366-1216 and GS-US-366-1160 due to the different prior treatment regimens evaluated. Across studies, data from a total of 754 subjects who received ODE are summarized (see below for Study GS-US-366-1216 and Module 2.7.3 Summary of Clinical Efficacy for Study GS-US-366-1160), with the following median (first quartile [Q1], third quartile [Q3]) durations of exposure to ODE:

- Study GS-US-366-1216: 47.9 (43.7, 59.1) weeks (N = 316)
- Study GS-US-366-1160: 47.9 (43.4, 59.1) weeks (N = 438)

## Table 1. Studies Supporting Clinical Safety

| Study | Study Design | Number of Subjects[a] by Treatment Regimens | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| **HIV-Infected, Virologically Suppressed Adults** | | | | |
| GS-US-366-1216 | Phase 3b randomized, double-blind, multicenter study to evaluate the efficacy, safety, and tolerability of switching to ODE from CPA | Switch to ODE (N = 316)<br>Stay on CPA (N = 314) | Week 48 efficacy and safety | **CSR:**<br>GS-US-366-1216 Week 48<br>**Narrative:**<br>m2.7.3, Section 2.1 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

### 1.1.2. Safety Assessments

Safety assessments for Study GS-US-366-1216 are described in this section.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0. Adverse events described in text were treatment-emergent and are referred to as AEs. The investigator was responsible for final review and confirmation of accuracy of events, relationship, and severity, documented by the signature on the electronic case report form.

Bone safety was assessed as follows:

- Fracture events were reviewed by the Gilead Sciences (Gilead) medical monitors prior to database lock, based on the Standardized MedDRA Query of osteoporosis/osteopenia and the MedDRA high-level group term of fractures for Study GS-US-366-1216
- Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry (DXA) scan
- The following bone laboratory parameters were assessed: procollagen type 1 N-terminal propeptide (P1NP), type I collagen C-terminal telopeptide (CTx), and parathyroid hormone (PTH)

The following renal laboratory parameters were assessed: serum creatinine, estimated glomerular filtration rate, proteinuria by dipstick, urine protein to creatinine ratio (UPCR), urine albumin to creatinine ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, and beta-2-microglobulin (β2M) to creatinine ratio.

Laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that required medical or surgical intervention or led to study drug interruption, modification or discontinuation were recorded as AEs or SAEs, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiograms [ECGs], x-rays, vital signs) associated with signs and/or symptoms were recorded as AEs or SAEs if they met the definitions. Laboratory abnormalities were graded according to toxicity criteria specified in the respective study protocol.

### 1.1.3. Narratives of Safety Studies

Narrative safety data from Study GS-US-366-1216 is presented in m2.7.3, Section 2.

## 1.2. Overall Extent of Exposure

Disposition for subjects in Study GS-US-366-1216 is described in m2.7.3, Section 3.1.

### 1.2.1. Clinical Studies

Duration of exposure for subjects in Study GS-US-366-1216 is summarized in Table 2 and described in detail in the Clinical Study Report (CSR; Study GS-US-366-1216 Week 48, Section 11.1).

Median (Q1, Q3) duration of exposure to study drug was 47.9 (43.7, 59.1) weeks in the ODE group and 48.0 (43.7, 50.1) weeks in the CPA group.

**Table 2. GS-US-366-1216: Duration of Exposure to Study Drug (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) |
|---|---|---|
| Total Exposure to Study Drug (Weeks) | | |
| N | 316 | 314 |
| Mean (SD) | 48.3 (9.78) | 47.9 (9.68) |
| Median | 47.9 | 48.0 |
| Q1, Q3 | 43.7, 59.1 | 43.7, 50.1 |
| Min, Max | 1.1, 72.0 | 1.9, 63.4 |
| Total Exposure to Study Drug | | |
| ≥ 4 Weeks (28 days) | 315 (99.7%) | 312 (99.4%) |
| ≥ 8 Weeks (56 days) | 312 (98.7%) | 311 (99.0%) |
| ≥ 12 Weeks (84 days) | 312 (98.7%) | 309 (98.4%) |
| ≥ 24 Weeks (168 days) | 307 (97.2%) | 304 (96.8%) |
| ≥ 36 Weeks (252 days) | 301 (95.3%) | 302 (96.2%) |
| ≥ 48 Weeks (336 days) | 156 (49.4%) | 163 (51.9%) |
| ≥ 60 Weeks (420 days) | 63 (19.9%) | 55 (17.5%) |
| ≥ 72 Weeks (504 days) | 1 (0.3%) | 0 |

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.
If the last dose date was completely missing, or only the year was known, or for subjects still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date; in the case where the last study drug end date was nonmissing, it was used to impute the last dose date.
Source: GS-US-366-1216 Week 48, Table 15.11.1.1

### 1.2.2. Postmarketing Data

Odefsey was first approved for the treatment of HIV-1 infection in patients 12 years of age and older in the US on 01 March 2016. As of 31 May 2016, cumulative patient exposure to ODE was estimated to be 1638 patient-years.

## 1.3. Demographic and Other Characteristics of Study Population

### 1.3.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics of subjects in Study GS-US-366-1216 are described in detail in the CSR (GS-US-366-1216 Week 48, Section 8.3.1).

Demographic and baseline characteristics were similar between the 2 treatment groups with the exception of sex; a higher percentage of subjects in the ODE group (13.0%, 41 subjects) compared with the CPA group (8.0%, 25 subjects) were female (p = 0.040; Table 3). Most subjects were male (89.5%), either white (75.1%) or black (18.9%), and not Hispanic/Latino (85.1%). Median and mean age was 45 years (range: 23 to 72). Median (Q1, Q3) body mass index (BMI) at baseline was 25.5 (23.1, 28.4) kg/$m^2$.

**Table 3. GS-US-366-1216: Demographic and Baseline Characteristics (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) | Total (N = 630) | ODE vs CPA P-Value |
|---|---|---|---|---|
| Age (Years) | | | | |
| N | 316 | 314 | 630 | 0.12 |
| Mean (SD) | 45 (10.4) | 44 (10.2) | 45 (10.3) | |
| Median | 46 | 44 | 45 | |
| Q1, Q3 | 37, 53 | 36, 51 | 37, 52 | |
| Min, Max | 23, 72 | 23, 71 | 23, 72 | |
| Sex at Birth | | | | |
| Male | 275 (87.0%) | 289 (92.0%) | 564 (89.5%) | 0.040 |
| Female | 41 (13.0%) | 25 (8.0%) | 66 (10.5%) | |
| Race | | | | |
| American Indian or Alaska Native | 1 (0.3%) | 2 (0.6%) | 3 (0.5%) | 0.26 |
| Asian | 7 (2.2%) | 17 (5.4%) | 24 (3.8%) | |
| Black | 65 (20.6%) | 54 (17.2%) | 119 (18.9%) | |
| Native Hawaiian or Pacific Islander | 0 | 1 (0.3%) | 1 (0.2%) | |
| White | 238 (75.3%) | 235 (74.8%) | 473 (75.1%) | |
| Not Permitted | 0 | 0 | 0 | |
| Other | 5 (1.6%) | 5 (1.6%) | 10 (1.6%) | |
| Ethnicity | | | | |
| Hispanic or Latino | 40 (12.7%) | 53 (16.9%) | 93 (14.8%) | 0.14 |
| Not Hispanic or Latino | 275 (87.0%) | 261 (83.1%) | 536 (85.1%) | |
| Not Permitted | 1 (0.3%) | 0 | 1 (0.2%) | |

| | ODE (N = 316) | CPA (N = 314) | Total (N = 630) | ODE vs CPA P-Value |
|---|---|---|---|---|
| Baseline Body Mass Index (kg/m$^2$) | | | | |
| N | 316 | 314 | 630 | 0.13 |
| Mean (SD) | 26.7 (5.05) | 25.9 (4.43) | 26.3 (4.76) | |
| Median | 25.7 | 25.5 | 25.5 | |
| Q1, Q3 | 23.3, 29.0 | 23.0, 27.8 | 23.1, 28.4 | |
| Min, Max | 17.7, 47.8 | 16.5, 46.8 | 16.5, 47.8 | |

The denominator for percentage is the number of subjects in the Safety Analysis Set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data).
For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
For Subject 10067-1459, collection of ethnicity information was "not permitted". The subject was excluded from the CMH test.
Not Permitted = local regulators did not allow collection of race or ethnicity information.
Body mass index (kg/m^2) = [Weight (kg)/Height (cm)^2]*10,000.
Source: GS-US-366-1216 Week 48, Table 15.8.3.1

### 1.3.2. Baseline Disease Characteristics

Baseline disease characteristics of subjects in Study GS-US-366-1216 are summarized in Table 4 and described in detail in the CSR (Study GS-US-366-1216 Week 48, Section 8.3.2).

Baseline disease characteristics were similar between the 2 treatment groups with the exception of HIV-1 RNA categories; a higher percentage of subjects in the ODE group (2.8%, 9 subjects) compared with the CPA group (0.6%, 2 subjects) had HIV-1 RNA ≥ 50 copies/mL (p = 0.034). Overall, 98.3% of subjects had baseline HIV-1 RNA < 50 copies/mL. Median (Q1, Q3) baseline CD4 cell count was 670 (521, 856) cells/µL, and the mean (SD) baseline CD4 cell count was 709 (271.7) cells/µL (range: 104 to 2527). The most common HIV risk factor category was homosexual sex (79.5%); 18.3% of subjects reported heterosexual sex as the mode of infection.

Median estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) was similar between the 2 treatment groups. Median (Q1, Q3) baseline $eGFR_{CG}$ was 102.4 (88.0, 119.8) mL/min. Most subjects (90.5%) had no proteinuria by urinalysis (dipstick).

**Table 4. GS-US-366-1216: Baseline Disease Characteristics (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) | Total (N = 630) | ODE vs CPA P-Value |
|---|---|---|---|---|
| HIV-1 RNA Categories (copies/mL) | | | | |
| < 50 | 307 (97.2%) | 312 (99.4%) | 619 (98.3%) | 0.034 |
| ≥ 50 | 9 (2.8%) | 2 (0.6%) | 11 (1.7%) | |
| CD4 Cell Count (/μL) | | | | |
| N | 316 | 314 | 630 | 0.77 |
| Mean (SD) | 711 (278.9) | 707 (264.7) | 709 (271.7) | |
| Median | 673 | 668 | 670 | |
| Q1, Q3 | 521, 877 | 525, 817 | 521, 856 | |
| Min, Max | 104, 2527 | 186, 1807 | 104, 2527 | |
| CD4 Cell Count Categories (/μL) | | | | |
| < 50 | 0 | 0 | 0 | 0.92 |
| ≥ 50 to < 200 | 5 (1.6%) | 1 (0.3%) | 6 (1.0%) | |
| ≥ 200 to < 350 | 10 (3.2%) | 16 (5.1%) | 26 (4.1%) | |
| ≥ 350 to < 500 | 52 (16.5%) | 50 (15.9%) | 102 (16.2%) | |
| ≥ 500 | 249 (78.8%) | 247 (78.7%) | 496 (78.7%) | |
| CD4 Percentage (%) | | | | |
| N | 316 | 314 | 630 | 0.054 |
| Mean (SD) | 37.1 (8.83) | 35.7 (8.71) | 36.4 (8.79) | |
| Median | 37.6 | 35.9 | 36.8 | |
| Q1, Q3 | 31.7, 42.4 | 30.7, 41.3 | 31.2, 41.9 | |
| Min, Max | 11.7, 60.7 | 8.5, 60.4 | 8.5, 60.7 | |
| Mode of Infection (HIV Risk Factors) | | | | |
| Heterosexual Sex | 66 (20.9%) | 49 (15.6%) | 115 (18.3%) | |
| Homosexual Sex | 246 (77.8%) | 255 (81.2%) | 501 (79.5%) | |
| IV Drug Use | 6 (1.9%) | 9 (2.9%) | 15 (2.4%) | |
| Transfusion | 2 (0.6%) | 1 (0.3%) | 3 (0.5%) | |
| Vertical Transmission | 0 | 0 | 0 | |
| Other | 6 (1.9%) | 4 (1.3%) | 10 (1.6%) | |
| Unknown | 8 (2.5%) | 6 (1.9%) | 14 (2.2%) | |

| | ODE (N = 316) | CPA (N = 314) | Total (N = 630) | ODE vs CPA P-Value |
|---|---|---|---|---|
| HIV Disease Status | | | | |
| Asymptomatic | 277 (87.7%) | 278 (88.5%) | 555 (88.1%) | 0.73 |
| Symptomatic HIV Infection | 18 (5.7%) | 17 (5.4%) | 35 (5.6%) | |
| AIDS | 21 (6.6%) | 19 (6.1%) | 40 (6.3%) | |
| Unknown | 0 | 0 | 0 | |
| HBV Surface Antigen Status | | | | |
| Positive | 0 | 0 | 0 | N/A |
| Negative | 316 (100.0%) | 314 (100.0%) | 630 (100.0%) | |
| HCV Antibody Status | | | | |
| Positive | 18 (5.7%) | 20 (6.4%) | 38 (6.0%) | 0.72 |
| Negative | 298 (94.3%) | 294 (93.6%) | 592 (94.0%) | |
| Estimated Glomerular Filtration Rate by Cockcroft-Gault (mL/min) | | | | |
| N | 316 | 314 | 630 | 0.47 |
| Mean (SD) | 106.1 (26.18) | 106.2 (29.88) | 106.2 (28.06) | |
| Median | 103.5 | 99.7 | 102.4 | |
| Q1, Q3 | 88.5, 119.8 | 87.3, 119.8 | 88.0, 119.8 | |
| Min, Max | 55.3, 219.0 | 45.9, 265.2 | 45.9, 265.2 | |
| Proteinuria by Urinalysis (dipstick) | | | | |
| Grade 0 | 285 (90.2%) | 285 (90.8%) | 570 (90.5%) | 0.92 |
| Grade 1 | 31 (9.8%) | 28 (8.9%) | 59 (9.4%) | |
| Grade 2 | 0 | 1 (0.3%) | 1 (0.2%) | |
| Grade 3 | 0 | 0 | 0 | |

N/A = not applicable
The denominator for percentage is the number of subjects in the Safety Analysis Set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Percentages may add to more than 100% for the HIV risk factor category and enrollment survey as a subject may provide more than 1 response.
For urine protein by dipstick, the highest grade is up to Grade 3.
Source: GS-US-366-1216 Week 48, Table 15.8.3.2

# 2. ADVERSE EVENTS

## 2.1. Analysis of Adverse Events

Adverse events for subjects in Study GS-US-366-1216 are described in detail in the CSR (GS-US-366-1216 Week 48, Section 11.2).

Similar percentages of subjects in each group had an AE (ODE 80.4%, 254 of 316 subjects; CPA 80.9%, 254 of 314 subjects). A slightly higher percentage subjects in the ODE group than in the CPA group had a Grade 2, 3, or 4 AE (ODE 39.2%, 124 subjects; CPA 35.0%, 110 subjects), or an SAE (ODE 5.7%, 18 subjects; CPA 3.8%, 12 subjects) (Table 5).

A slightly higher percentage of subjects in the ODE group than in the CPA group had a Grade 3 or 4 AE (ODE 5.4%, 17 subjects; CPA 3.2%, 10 subjects). One subject in the ODE group had a study drug-related Grade 3 or 4 AE (ODE 0.3%). No subject in the CPA group had a study drug-related Grade 3 or 4 AE. No subject in either group had a study drug-related SAE.

Subjects who switched to ODE had a lower incidence of any AE considered by the investigator as related to study drug (ODE 6.3%, 20 subjects; CPA 11.8%, 37 subjects).

Adverse events that led to study drug discontinuation were uncommon in both groups (ODE 1.3%, 4 subjects; CPA 1.0%, 3 subjects). One subject in each group (0.3% in each group) died during the study. Both deaths were not considered related to study drug by the investigator.

**Table 5. GS-US-366-1216: Overall Summary of Adverse Events (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 254 (80.4%) | 254 (80.9%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 124 (39.2%) | 110 (35.0%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 17 (5.4%) | 10 (3.2%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 20 (6.3%) | 37 (11.8%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 7 (2.2%) | 10 (3.2%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 1 (0.3%) | 0 |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 18 (5.7%) | 12 (3.8%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 0 | 0 |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 4 (1.3%) | 3 (1.0%) |
| Subjects who had Treatment-Emergent Death | 1 (0.3%) | 1 (0.3%) |

Adverse events were coded using MedDRA version 19.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Treatment-emergent death refers to a death which occurred between the first dose date and the last dose date plus 30 days (inclusive).
Source: GS-US-366-1216 Week 48, Table 15.11.2.1.1

### 2.1.1. Common Adverse Events

Adverse events for subjects in Study GS-US-366-1216 are described in detail in the CSR (Study GS-US-366-1216 Week 48, Section 11.2).

The following were the most commonly reported AEs that occurred in ≥ 5% of subjects in either treatment group (Table 6):

- ODE: upper respiratory tract infection (8.5%, 27 of 316 subjects); diarrhea (7.3%, 23 subjects); and nasopharyngitis (7.0%, 22 subjects)
- CPA: upper respiratory tract infection (8.3%, 26 of 314 subjects); diarrhea (8.3%, 26 subjects); nasopharyngitis (7.6%, 24 subjects); bronchitis (5.7%, 18 subjects); sinusitis (5.7%, 18 subjects); and headache (5.4%, 17 subjects)

Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs.

No AE by preferred term (PT) was reported with a difference in percentages of ≥ 5% between groups.

**Table 6. GS-US-366-1216: Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) |
|---|---|---|
| Number of Subjects Experiencing Any Treatment-Emergent Adverse Event | 254 (80.4%) | 254 (80.9%) |
| Gastrointestinal disorders | 80 (25.3%) | 68 (21.7%) |
| Diarrhea | 23 (7.3%) | 26 (8.3%) |
| Infections and infestations | 140 (44.3%) | 149 (47.5%) |
| Bronchitis | 12 (3.8%) | 18 (5.7%) |
| Upper respiratory tract infection | 27 (8.5%) | 26 (8.3%) |
| Nasopharyngitis | 22 (7.0%) | 24 (7.6%) |
| Sinusitis | 12 (3.8%) | 18 (5.7%) |
| Nervous system disorders | 30 (9.5%) | 36 (11.5%) |
| Headache | 15 (4.7%) | 17 (5.4%) |

Adverse events were coded using MedDRA version 19.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
System organ class (SOC) and high level term (within each SOC) were presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-366-1216 Week 48, Table 15.11.2.1.2

### Adverse Events by Severity

Most AEs reported in either treatment group of Study GS-US-366-1216 were Grade 1 or 2 in severity (Table 5). A slightly higher percentage of subjects in the ODE group than in the CPA group had a Grade 3 or 4 AE (ODE 5.4%, 17 subjects; CPA 3.2%, 10 subjects); most of these subjects had no Grade 4 events, but rather had AEs that were Grade 3 as worst severity (ODE 14 of 17 subjects; CPA 8 of 10 subjects). No pattern was observed in the type of Grade 3 or 4 events. Grade 4 events occurred in approximately 1% of subjects in both groups.

No Grade 3 or 4 AEs by PT were reported for ≥ 1% of subjects in either group.

### Adverse Events Considered Related to Study Drug

A lower percentage of subjects in the ODE group than in the CPA group had any AE considered by the investigator as related to study drug in Study GS-US-366-1216 (ODE 6.3%, 20 subjects; CPA 11.8%, 37 subjects).

The most common AEs considered related to study drug by the investigator, reported for ≥ 1% of subjects in either group were as follows:

- ODE: No study drug-related AE was reported for ≥ 1% of subjects
- CPA: abnormal dreams (1.9%, 6 subjects), diarrhea (1.6%, 5 subjects), and nausea (1.0%, 3 subjects)

### 2.1.2. Deaths

One subject in each study group died during Study GS-US-366-1216. None of the events leading to death were considered related to study drug by the investigator. Causes of death were cardiac arrest in the ODE group and carbon monoxide poisoning in the CPA group.

### 2.1.3. Other Serious Adverse Events

Serious AEs were reported for a higher percentage of subjects in the ODE group than CPA group in Study GS-US-366-1216 (ODE 5.7%, 18 subjects; CPA 3.8%, 12 subjects) (GS-US-366-1216 Week 48, Section 11.5).

The only SAEs occurring in > 1 subject in either treatment group were osteomyelitis and pulmonary embolism, both reported in 2 subjects (0.6%) in the ODE group, and asthma, reported in 2 subjects (0.6%) in the CPA group.

No SAE was considered related to study drug by the investigator.

### 2.1.4. Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section.

Few subjects in either group in Study GS-US-366-1216 discontinued study drug due to AEs (ODE 1.3%, 4 subjects; CPA 1.0%, 3 subjects) (GS-US-366-1216 Week 48, Section 11.6). Most AEs leading to discontinuation of study drugs were nonserious, and none were reported for > 1 subject in either treatment group. One subject in each group had 1 study drug-related AE leading to study drug discontinuation.

### 2.1.5. Analysis of Adverse Events by Organ System or Syndrome

#### 2.1.5.1. Bone Safety

Bone safety for subjects in Study GS-US-366-1216 is described in detail in the CSR (Study GS-US-366-1216 Week 48, Section 11.2.4.1).

##### 2.1.5.1.1. Fracture Events

The percentages of subjects with fracture events were comparable between treatment groups in Study GS-US-366-1216 (ODE 1.3%, 4 subjects; CPA 1.6%, 5 subjects; p = 0.750). In the ODE group, 1 of the fracture events was reported as an SAE: radius fracture. All the other fracture

events were nonserious. When finger and toe fractures were excluded all other fracture events were the result of trauma and considered by the investigator as unrelated to the study drug; none resulted in permanent discontinuation of study drug.

#### 2.1.5.1.2. Percentage Change from Baseline in Hip and Spine BMD

There were increases from baseline in hip and spine BMD in the ODE group compared with minimal changes from baseline in both parameters in the CPA group in Study GS-US-366-1216 ($p < 0.001$ for the differences between groups at Weeks 24 and 48) (Table 7).

Mean (SD) percentage changes from baseline in hip and spine BMD at Week 48 (observed data) were as follows:

- Hip
  - ODE: 1.040% (1.9404%)
  - CPA: −0.245% (2.0805%)
- Spine
  - ODE: 1.613% (3.4346%)
  - CPA: 0.075% (2.9605%)

**Table 7. GS-US-366-1216: Percentage Change from Baseline in Hip and Spine BMD by Visit (Observed Data; Hip or Spine DXA Analysis Set)**

| | | | | ODE vs CPA | |
|---|---|---|---|---|---|
| | Statistic | ODE | CPA | P-Value | Difference in LSM (95% CI) |
| **Hip BMD** | | | | | |
| Baseline (g/cm$^2$) | N | 184 | 173 | 0.94 | 0.001 (−0.028, 0.030) |
| | Mean (SD) | 0.991 (0.1393) | 0.990 (0.1421) | | |
| % Change at Week 24 | N | 175 | 171 | < 0.001 | 0.761 (0.360, 1.163) |
| | Mean (SD) | 0.771 (1.8243) | 0.009 (1.9735) | | |
| % Change at Week 48 | N | 168 | 165 | < 0.001 | 1.285 (0.851, 1.718) |
| | Mean (SD) | 1.040 (1.9404) | −0.245 (2.0805) | | |
| **Spine BMD** | | | | | |
| Baseline (g/cm$^2$) | N | 187 | 176 | 0.80 | 0.005 (−0.032, 0.041) |
| | Mean (SD) | 1.088 (0.1766) | 1.084 (0.1753) | | |
| % Change at Week 24 | N | 178 | 174 | < 0.001 | 1.909 (1.332, 2.486) |
| | Mean (SD) | 1.766 (2.7870) | −0.142 (2.7175) | | |
| % Change at Week 48 | N | 172 | 168 | < 0.001 | 1.538 (0.853, 2.222) |
| | Mean (SD) | 1.613 (3.4346) | 0.075 (2.9605) | | |

% Change = Change from baseline at a postbaseline visit / baseline × 100%
P-values, difference in LSMs, and its 95% CI were from the ANOVA model including treatment as a fixed effect.
Source: GS-US-366-1216 Week 48, Tables 15.11.2.4.1.2 and 15.11.2.4.1.4

### Categorical Distribution of Percentage Change from Baseline in BMD

Differences between the 2 treatment groups in the categorical distribution of percentage change from baseline in hip, spine, and femoral neck BMD were statistically significant at Weeks 24 and 48 in Study GS-US-366-1216 ($p < 0.001$). There was evidence for an improvement in BMD after switching to ODE.

The percentages of subjects with ≥ 3% increases from baseline in hip and spine BMD at Week 48 were higher in the ODE group than in the CPA group, as follows (Table 8):

- Hip
  - ODE: 16.1%
  - CPA: 4.2%
- Spine
  - ODE: 27.3%
  - CPA: 11.3%

The percentages of subjects with ≥ 3% decreases from baseline in hip and spine BMD at Week 48 were lower in the ODE group than in the CPA group, as follows:

- Hip
  - ODE: 3.0%
  - CPA: 6.7%
- Spine
  - ODE: 6.4%
  - CPA: 13.1%

The percentages of subjects with ≥ 7% decreases from baseline in femoral neck BMD or ≥ 5% decreases from baseline in spine BMD at Week 48 were also lower in the ODE group (0.0% and 1.7%, respectively) than in the CPA group (1.2% and 3.0%, respectively) ($p < 0.001$ for the difference between groups at Week 48).

**Table 8. GS-US-366-1216: Percentage Change from Baseline in Hip and Spine BMD by Visit (Observed Data; Hip or Spine DXA Analysis Set)**

| | Visit | ODE n/N (%) | CPA n/N (%) |
|---|---|---|---|
| **Hip BMD** | | | |
| ≥ 3% Decrease | Week 24 | 4/175 (2.3%) | 7/171 (4.1%) |
| | Week 48 | 5/168 (3.0%) | 11/165 (6.7%) |
| No Decrease (≥ 0% Change) | Week 24 | 115/175 (65.7%) | 81/171 (47.4%) |
| | Week 48 | 119/168 (70.8%) | 76/165 (46.1%) |
| ≥ 3% Increase | Week 24 | 21/175 (12.0%) | 10/171 (5.8%) |
| | Week 48 | 27/168 (16.1%) | 7/165 (4.2%) |
| **Spine BMD** | | | |
| ≥ 3% Decrease | Week 24 | 5/178 (2.8%) | 20/174 (11.5%) |
| | Week 48 | 11/172 (6.4%) | 22/168 (13.1%) |
| No Decrease (≥ 0% Change) | Week 24 | 130/178 (73.0%) | 71/174 (40.8%) |
| | Week 48 | 115/172 (66.9%) | 87/168 (51.8%) |
| ≥ 3% Increase | Week 24 | 55/178 (30.9%) | 20/174 (11.5%) |
| | Week 48 | 47/172 (27.3%) | 19/168 (11.3%) |

Source: GS-US-366-1216 Week 48, Tables 15.11.2.4.1.6 and 15.11.2.4.1.7

#### 2.1.5.1.3. Bone Laboratory Parameters

Serum levels of PTH and CTx decreased from baseline in the ODE group and increased from baseline in the CPA group at Week 48 in Study GS-US-366-1216 ($p < 0.001$ for the differences between groups). Serum levels of P1NP decreased from baseline in both the ODE and CPA groups at Week 48, with a greater decrease from baseline in the ODE group than in the CPA group ($p < 0.001$ for the difference between groups). Median (Q1, Q3) percentage changes from baseline in PTH, CTx, and P1NP at Week 48 were as follows:

- PTH
  - ODE: –5.6% (–24.7%, 15.3%)
  - CPA: 10.8% (–14.2%, 37.5%)
- CTx
  - ODE: –2.4% (–16.7%, 12.8%)
  - CPA: 8.9% (–5.8%, 25.0%)
- P1NP
  - ODE: –30.48% (–41.33%, –16.40%)
  - CPA: –9.74% (–21.42%, 4.95%)

### 2.1.5.2. Renal Safety

Renal safety for subjects in Study GS-US-366-1216 is described in detail in the CSR (Study GS-US-366-1216 Week 48, Section 11.2.4.2).

#### 2.1.5.2.1. Renal Events

In the ODE group in Study GS-US-366-1216, 1 subject had a renal SAE (acute kidney injury) that was considered unrelated to study drug. The subject's concurrent medical condition included rhabdomyolysis, recreational drug use, pneumonia, and suicidal ideation. In the CPA group, no subject had a renal SAE.

No subject in either group discontinued study drug due to a renal AE. There were no cases of proximal renal tubulopathy (including Fanconi syndrome) reported during the study.

#### 2.1.5.2.2. Renal Laboratory Parameters

##### 2.1.5.2.2.1. Serum Creatinine

At Week 48 similar slight decreases from baseline in creatinine occurred in both the ODE and CPA groups in Study GS-US-366-1216 (Table 9). The difference between groups in the change from baseline in serum creatinine was not statistically significant at any time point except for Week 12 (p = 0.014 for the difference between groups at Week 12).

**Table 9. GS-US-366-1216: Change from Baseline in Serum Creatinine (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) | P-Value |
|---|---|---|---|
| Baseline (mg/dL) | | | |
| N | 316 | 314 | 0.21 |
| Mean (SD) | 1.02 (0.177) | 1.03 (0.168) | |
| Median | 1.00 | 1.02 | |
| Q1, Q3 | 0.88, 1.13 | 0.92, 1.15 | |
| Change at Week 48 (mg/dL) | | | |
| N | 299 | 293 | 0.67 |
| Mean (SD) | −0.02 (0.108) | −0.02 (0.112) | |
| Median | −0.02 | −0.01 | |
| Q1, Q3 | −0.09, 0.05 | −0.08, 0.05 | |

Baseline value was the last available value collected on or prior to first dose date of study drug.
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-366-1216 Week 48, Table 15.11.2.4.2.1

##### 2.1.5.2.2.2. Estimated Glomerular Filtration Rate

Small increases from baseline in $eGFR_{CG}$ were observed in the ODE group at Week 4 and persisted through Week 48, compared with minimal changes from baseline in the CPA group in Study GS-US-366-1216 (p = 0.002 for the difference between groups at Week 48) (Table 10).

**Table 10. GS-US-366-1216: Change from Baseline in $eGFR_{CG}$ (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) | P-Value |
|---|---|---|---|
| Baseline (mL/min) | | | |
| N | 316 | 314 | 0.47 |
| Mean (SD) | 106.1 (26.18) | 106.2 (29.88) | |
| Median | 103.5 | 99.7 | |
| Q1, Q3 | 88.5, 119.8 | 87.3, 119.8 | |
| Change at Week 48 (mL/min) | | | |
| N | 299 | 293 | 0.002 |
| Mean (SD) | 4.4 (13.93) | 1.1 (12.75) | |
| Median | 4.5 | 0.7 | |
| Q1, Q3 | −4.1, 12.3 | −6.6, 8.1 | |

Baseline value was the last available value collected on or prior to first dose date of study drug.
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-366-1216 Week 48, Table 15.11.2.4.2.2

2.1.5.2.2.3. Proteinuria by Urinalysis (Dipstick)

The majority of subjects in both treatment groups in Study GS-US-366-1216 had no proteinuria (Grade 0 by dipstick) at baseline and through Week 48. The percentage of subjects with improvement from baseline (toxicity grade decreased at least 1 grade from baseline) in proteinuria toxicity grade at Week 48 was higher in the ODE group than in the CPA group, as follows:

- ODE: 89.3% (25 of 28 subjects)
- CPA: 75.0% (21 of 28 subjects)

The percentage of subjects with proteinuria grade worsening from baseline at Week 48 was lower in the ODE group than in the CPA group, as follows:

- ODE: 3.7% (11 of 295 subjects)
- CPA: 4.8% (14 of 294 subjects)

2.1.5.2.2.4. Proteinuria by Quantitative Assessment

Decreases from baseline in UPCR and UACR were observed in the ODE group through Week 48 compared with mostly increases from baseline in the CPA group in Study GS-US-366-1216 ($p < 0.001$ for the differences in percentage change from baseline between groups at Week 48) (Table 11).

**Table 11. GS-US-366-1216: Change from Baseline in UPCR and UACR (Safety Analysis Set)**

| | ODE (N = 316) | | | CPA (N = 314) | | | |
|---|---|---|---|---|---|---|---|
| | N | Median (Q1, Q3) | Median (Q1, Q3) % Change from Baseline | N | Median (Q1, Q3) | Median (Q1, Q3) % Change from Baseline | P-Value |
| UPCR (mg/g) at Baseline | 316 | 53.2 (35.5, 88.7) | — | 314 | 50.0 (36.4, 80.6) | — | 0.69 |
| At Week 48 | 298 | 41.9 (28.7, 65.0) | −18.8% (−47.4%, 26.8%) | 294 | 50.7 (34.5, 88.2) | 7.3% (−31.4%, 63.0%) | < 0.001 |
| UACR (mg/g) at Baseline | 316 | 5.5 (3.7, 10.0) | — | 314 | 5.4 (3.8, 9.2) | — | 0.98 |
| At Week 48 | 298 | 5.1 (3.7, 8.5) | −7.8% (−34.2%, 27.6%) | 293 | 6.3 (4.2, 9.7) | 16.8% (−19.6%, 64.0%) | < 0.001 |

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-366-1216 Week 48, Tables 15.11.2.4.2.4 and 15.11.2.4.2.5

Most subjects in both treatment groups had no clinically significant proteinuria (UPCR > 200 mg/g) or albuminuria (UACR ≥ 30 mg/g) at baseline and through Week 48.

2.1.5.2.2.5. Proximal Tubular Proteinuria Assessments

Decreases from baseline in urine RBP to creatinine ratio and urine β2M to creatinine ratio at Weeks 24 and 48 were observed in the ODE group compared with increases, or smaller decreases, for subjects who remained on CPA in Study GS-US-366-1216 ($p < 0.001$ for the differences in percentage change from baseline between groups at Week 48) (Table 12).

**Table 12. GS-US-366-1216: Changes from Baseline in Urine RBP to Creatinine Ratio and Urine β2M to Creatinine Ratio (Safety Analysis Set)**

| | ODE (N = 316) | | | | CPA (N = 314) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median (Q1, Q3) | N[a] | Median (Q1, Q3) % Change from Baseline | N | Median (Q1, Q3) | N[a] | Median (Q1, Q3) % Change from Baseline |
| Urine RBP to Creatinine Ratio (µg/g) at Baseline | 313 | 101.2 (70.5, 157.6) | — | — | 310 | 111.1 (75.8, 196.9) | — | — |
| At Week 48 | 299 | 84.4 (60.8, 124.4) | 296 | −18.0% (−43.7%, 19.6%) | 296 | 132.2 (89.4, 229.7) | 292 | 21.5% (−17.3%, 84.2%) |
| Urine β2M to Creatinine Ratio (µg/g) at Baseline | 311 | 111.6 (67.0, 260.0) | — | — | 307 | 116.1 (61.7, 326.1) | — | — |
| At Week 48 | 296 | 80.8 (57.4, 121.7) | 291 | −29.0% (−63.8%, 10.8%) | 296 | 135.1 (69.1, 397.0) | 289 | 12.0% (−40.6%, 119.4%) |

a Number of subjects with nonmissing values at baseline and the specified study visit.
Source: GS-US-366-1216 Week 48, Tables 15.11.2.4.2.8 and 15.11.2.4.2.9

#### 2.1.5.3. HIV Symptoms Index Score

The HIV symptoms index score was not assessed in Study GS-US-366-1216.

## 2.2. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures, if applicable, are provided in the relevant CSRs.

# 3. CLINICAL LABORATORY EVALUATIONS

All laboratory abnormalities discussed in the following sections were treatment-emergent and are referred to as laboratory abnormalities.

## 3.1. Laboratory Abnormalities

Laboratory abnormalities for subjects in Study GS-US-366-1216 are described in detail in the CSR (GS-US-366-1216 Week 48, Section 11.7.3).

Most subjects had at least 1 laboratory abnormality reported during the study (ODE 86.3%, 272 of 315 subjects; CPA 79.6%, 249 of 313 subjects); most of the reported abnormalities were Grade 1 or Grade 2.

The incidence of laboratory abnormalities of any grade was similar between treatment groups for most chemistry, hematology, and urinalysis parameters. Overall, a higher percentage of subjects in the ODE group than the CPA group had Grade 3 or 4 abnormalities (ODE 12.7%, 40 subjects; CPA 6.1%, 19 subjects). This difference was predominantly due to the higher incidence of Grade 3 or 4 fasting low-density lipoprotein (LDL) and total cholesterol abnormalities in the ODE group (Table 13).

**Table 13. GS-US-366-1216: Grade 3 and 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) |
|---|---|---|
| Maximum Post-Baseline Toxicity Grade | 315 | 313 |
| Grade 3 | 34 (10.8%) | 13 (4.2%) |
| Grade 4 | 6 (1.9%) | 6 (1.9%) |
| Grade 3 or 4 | 40 (12.7%) | 19 (6.1%) |
| Chemistry | | |
| ALT | 315 | 313 |
| Grade 3 | 0 | 5 (1.6%) |
| Grade 4 | 1 (0.3%) | 1 (0.3%) |
| Grade 3 or 4 | 1 (0.3%) | 6 (1.9%) |
| AST | 315 | 313 |
| Grade 3 | 5 (1.6%) | 3 (1.0%) |
| Grade 4 | 0 | 1 (0.3%) |
| Grade 3 or 4 | 5 (1.6%) | 4 (1.3%) |

| | ODE (N = 316) | CPA (N = 314) |
|---|---|---|
| Creatine Kinase | 315 | 313 |
| Grade 3 | 9 (2.9%) | 2 (0.6%) |
| Grade 4 | 5 (1.6%) | 4 (1.3%) |
| Grade 3 or 4 | 14 (4.4%) | 6 (1.9%) |
| Serum Glucose (Nonfasting, Hyperglycemia) | 314 | 311 |
| Grade 3 | 3 (1.0%) | 2 (0.6%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 3 (1.0%) | 2 (0.6%) |
| Total Cholesterol (Fasting, Hypercholesterolemia) | 307 | 303 |
| Grade 3 | 3 (1.0%) | 0 |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 3 (1.0%) | 0 |
| LDL (Fasting) | 307 | 303 |
| Grade 3 | 12 (3.9%) | 2 (0.7%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 12 (3.9%) | 2 (0.7%) |
| Urinalysis | | |
| Urine Glucose (Glycosuria) | 315 | 313 |
| Grade 3 | 5 (1.6%) | 2 (0.6%) |
| Grade 4 | 0 | 0 |
| Grade 3 or 4 | 5 (1.6%) | 2 (0.6%) |

The denominator for percentage is the number of subjects in the safety analysis set with at least 1 postbaseline value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
For urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
For nonfasting serum glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting serum glucose test was not done for all subjects at baseline.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Source: GS-US-366-1216 Week 48, Table 15.11.6.4.2

## 3.2. Liver-Related Laboratory Parameters

In the assessment of liver enzyme elevations in relation to normal ranges in Study GS-US-366-1216, no subject had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN), total bilirubin > 2 × ULN, and alkaline phosphatase < 2 × ULN. No Hy's Law cases were identified.

### 3.3. Metabolic Laboratory Parameters

Metabolic laboratory parameters for subjects in Study GS-US-366-1216 are described in detail in the CSR (GS-US-366-1216 Week 48, Section 11.7.5).

There were increases from baseline in fasting values of total cholesterol, direct LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in the ODE group, while these parameters had little change or slightly decreased in the CPA group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups in change from baseline at Weeks 24 and 48; Table 14). There were no clinically significant changes from baseline in the fasting values for the total cholesterol to HDL ratio or glucose for either treatment group. Findings were similar when the analysis excluded subjects who were taking lipid-modifying medications (GS-US-366-1216 Week 48, Tables 15.11.6.3.9 to 15.11.6.3.13).

**Table 14. GS-US-366-1216: Changes from Baseline in Fasting Metabolic Assessments at Week 48 (Safety Analysis Set)**

| | ODE (N = 316) | | CPA (N = 314) | |
|---|---|---|---|---|
| **Metabolic Assessment** | **N** | **Mean (SD)** | **N** | **Mean (SD)** |
| Fasting Total Cholesterol (mg/dL) | | | | |
| Baseline | 305 | 175 (33.4) | 309 | 170 (32.4) |
| Change at Week 48 | 285 | 15 (28.8) | 290 | 0 (25.1) |
| Fasting Direct LDL Cholesterol (mg/dL) | | | | |
| Baseline | 305 | 110 (30.0) | 309 | 106 (28.5) |
| Change at Week 48 | 285 | 12 (24.0) | 290 | 1 (20.6) |
| Fasting HDL Cholesterol (mg/dL) | | | | |
| Baseline | 305 | 49 (13.2) | 309 | 48 (14.0) |
| Change at Week 48 | 285 | 3 (8.7) | 290 | 0 (7.7) |
| Fasting Total Cholesterol to HDL Ratio | | | | |
| Baseline | 305 | 3.8 (1.18) | 309 | 3.8 (1.29) |
| Change at Week 48 | 285 | 0.1 (0.69) | 290 | 0.1 (1.12) |
| Fasting Triglycerides (mg/dL) | | | | |
| Baseline | 305 | 124 (80.3) | 309 | 121 (78.4) |
| Change at Week 48 | 285 | 10 (73.6) | 290 | −9 (58.5) |
| Fasting Glucose (mg/dL) | | | | |
| Baseline | 304 | 94 (13.0) | 308 | 95 (14.8) |
| Change at Week 48 | 285 | 2 (16.6) | 290 | 1 (16.9) |

Only laboratory measurements under fasting status were summarized.
Baseline value was the last available value collected on or prior to first dose date of study drug.
Source: GS-US-366-1216 Week 48, Tables 15.11.6.3.1 to 15.11.6.3.6

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Detailed information on vital signs, physical findings, and other observations related to safety may be found in the CSR for the study (GS-US-366-1216 Week 48, Section 11.8). Results of safety ECG assessments are described in this section for Study GS-US-366-1216, along with changes from baseline in body weight.

## 4.1. Electrocardiogram

Among subjects who had ECG results available at Baseline and Week 24 or 48 in Study GS-US-366-1216, clinically significant ECG findings were reported at Week 24 for 5 of 303 subjects (1.7%) in the ODE group and no subject in the CPA group, and at Week 48 for 1 of 295 subjects (0.3%) in the ODE group and 1 of 297 subjects (0.3%) in the CPA group. The subject in the ODE group that had a clinically significant ECG finding at Week 48 also had a clinically significant abnormality at Week 24. Of these ECG findings, 1 was reported as an AE (abnormal ECG) for a subject in the ODE group. This AE was nonserious, Grade 1 in severity, considered unrelated to study drug by the investigator, and did not result in study drug discontinuation. There were no other AEs related to ECG findings.

In the GS-US-366-1216 CSR the number of the subjects in the ODE group having clinically significant ECG findings was incorrectly reported as 4 subjects. This should have been 5 subjects as described above. This will be corrected when the next CSR is written.

## 4.2. Body Weight

There were no clinically relevant changes from baseline or between treatment groups in median values for body weight in either treatment group in Study GS-US-366-1216.

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

For subjects who switched from CPA (Study GS-US-366-1216), AE incidence was analyzed by sex, age, and race. The results of these analyses are described in the CSR (GS-US-366-1216 Week 48, Section 11.3)

The AEs associated with ODE in Study GS-US-366-1216 were higher in males than females, higher among subjects < 50 years than those ≥ 50 years, and lower in black than nonblack subjects. Overall, the AE profile for ODE was similar across the subgroups of sex, age, and race, acknowledging the small numbers of subjects in some subgroups, as described below.

### 5.1.1. Sex

The percentages of subjects experiencing any AE in Study GS-US-366-1216 were higher in males than females in both treatment groups (ODE: male 81.5%, 224 of 275 subjects; female 73.2%, 30 of 41 subjects; CPA: male 81.3%, 235 of 289; female 76.0%, 19 of 25 subjects).

### 5.1.2. Age

The percentages of subjects with any AE in Study GS-US-366-1216 were higher among those < 50 years than those ≥ 50 years in the ODE group (< 50 years 82.7%, 163 of 197 subjects; ≥ 50 years 76.5%, 91 of 119 subjects) and comparable in subjects < 50 and ≥ 50 years in the CPA group (< 50 years 81.1%, 172 of 212 subjects; ≥ 50 years 80.4%, 82 of 102 subjects).

### 5.1.3. Race

The percentages of subjects experiencing any AE in Study GS-US-366-1216 were lower among black than nonblack in the ODE group (black 67.7%, 44 of 65 subjects; nonblack 83.7%, 210 of 251 subjects) but comparable in black and nonblack subjects in the CPA group (black 81.5%, 44 of 54 subjects; nonblack 80.8%, 210 of 260 subjects).

## 5.2. Extrinsic Factors

For subjects who switched from CPA (Study GS-US-366-1216), AE incidence was analyzed by region. The results of this analysis are described in the CSR (GS-US-366-1216 Week 48, Section 11.3). The AEs associated with ODE in Study GS-US-366-1216 were lower in subjects from the US than those from Ex-US regions. Overall, the AE profile for ODE was similar across the subgroup of region, as described below.

### 5.2.1. Region

The percentages of subjects experiencing any AE in Study GS-US-366-1216 were lower in subjects from the US than those from Ex-US regions in both treatment groups (ODE: US 78.4%, 174 of 222 subjects; Ex-US 85.1%, 80 of 94 subjects; CPA: US 77.4%, 175 of 226 subjects; Ex-US 89.8%, 79 of 88 subjects).

## 5.3. Drug Interactions

No new information is presented.

## 5.4. Use in Pregnancy and Lactation

A confirmed pregnancy was reported in 1 subject in the ODE group on Day 140 in Study GS-US-366-1216, and study drug was discontinued (GS-US-366-1216 Week 48, Listing 16.2.8.6). The subject had an SAE of pre-eclampsia on Day 306 and delivered a live male baby via Caesarean section on Day 314 at 31 weeks and 2 days of gestational age. The baby's hospitalization was prolonged due to premature birth but the baby did not receive any special treatment. The investigator considered the event of pre-eclampsia as unrelated to study drug.

## 5.5. Overdose

No new safety issues have been identified regarding overdose since the original marketing application.

## 5.6. Drug Abuse

No safety issues concerning the abuse or misuse of ODE tablets are anticipated from the available data.

## 5.7. Withdrawal and Rebound

No new information is presented.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No new information is presented.

# 6. POSTMARKETING DATA

Postmarketing safety data for ODE and its individual components are carefully evaluated on an ongoing basis for any new safety issues and the labeling changes are submitted to regulatory authorities when new adverse reactions are identified. There have been no newly identified adverse reactions for ODE based on the postmarketing data available to date.

# 7. REFERENCES

No references are included.

# 8. APPENDIX

No appendices are included.

**SECTION 2.7**
**CLINICAL SUMMARY**

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## SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

Gilead Sciences

26 October 2016

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ART | antiretroviral therapy |
| AST | aspartate aminotransferase |
| BMD | bone mineral density |
| CD | cluster determinant |
| CI | confidence interval |
| COBI, C | cobicistat (Tybost®) |
| CSR | clinical study report |
| DXA | dual-energy x-ray absorptiometry |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| $eGFR_{CKD\text{-}EPI,\ creatinine}$ | estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation |
| EVG, E | elvitegravir (Vitekta®) |
| $FEPO_4$ | fractional excretion of phosphate |
| FEUA | fractional excretion of uric acid |
| FTC, F | emtricitabine (Emtriva®) |
| GEN | Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; coformulated; previously referred to as E/C/F/TAF) |
| GFR | glomerular filtration rate |
| GGT | gamma-glutamyltransferase |
| Gilead | Gilead Sciences, Inc. |
| HDL | high-density lipoprotein |
| HGLT | high-level group term |
| HIV | human immunodeficiency virus |
| HIV-1 | human immunodeficiency virus type 1 |
| ISS | Integrated Summary of Safety |
| LDL | low-density lipoprotein |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N or n | number of subjects in a population (N) or subset (n) |
| N(t)RTI | nucleos(t)ide reverse transcriptase inhibitor |
| PT | preferred term |
| Q1, Q3 | first quartile, third quartile |
| RBC | red blood cell |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |

| | |
|---|---|
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SMQ | Standardized MedDRA Query |
| SOC | system organ class |
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TmP/GFR | renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate |
| UACR | urine albumin to creatinine ratio |
| UPCR | urine protein to creatinine ratio |
| US | United States |

# 1. EXPOSURE TO THE DRUG

Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) is an oral, once-daily, fixed-dose combination that provides a potent and well-tolerated regimen for the long-term treatment of patients infected with HIV-1. Genvoya contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG), the pharmacoenhancer cobicistat (COBI), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), and the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir alafenamide (TAF).

## 1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

This submission provides additional long-term efficacy and safety data for HIV-infected, antiretroviral therapy (ART)-naive adults in Studies GS-US-292-0104 and GS-US-292-0111 with results through 144 weeks of treatment with GEN (Table 1).

The pooling of data was specified in the protocol for each of the 2 pivotal Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 because the study designs and populations were identical, differing only in geography. For the integrated analysis, data were pooled by treatment group (GEN versus E/C/F/tenofovir disoproxil fumarate [TDF], coformulated; Stribild® [STB]) according to the randomized treatment received.

Clinical and laboratory adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0, with system organ class, high-level group term (HLGT), high level term, preferred term (PT), and lower-level term attached to the clinical database.

In this summary, all AEs discussed were treatment emergent and are referred to as AEs. All AEs were assessed by the investigator or qualified designee and recorded on the AE electronic case report form (eCRF). The AE entry indicated whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug or to a study procedure, the action taken with study drug due to the AE, and the severity of the AE. The investigator was responsible for final review and confirmation of accuracy of events, relationship, and severity, confirmed by the signature on the eCRF.

Renal safety was monitored through the evaluation of serum creatinine, estimated glomerular filtration rate (eGFR), proteinuria, urine protein to creatinine ratio (UPCR), urine albumin to creatinine ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, and other renal biomarkers (renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate [TmP/GFR], fractional excretion of phosphate [$FEPO_4$], and fractional excretion of uric acid [FEUA]).

**Table 1. Studies Supporting Clinical Safety for the Genvoya Submission**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| GS-US-292-0104 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GEN vs STB | GEN + placebo-to-match STB (N = 435)<br>STB + placebo-to-match GEN (N = 432) | Week 144 efficacy and safety | **CSR:** GS-US-292-0104 Week 144<br>**Narrative:** m2.7.3, Section 2.1 |
| GS-US-292-0111 | | GEN + placebo-to-match STB (N = 431)<br>STB + placebo-to-match GEN (N = 435) | | **CSR:** GS-US-292-0111 Week 144<br>**Narrative:** m2.7.3, Section 2.2 |

CSR = clinical study report; GEN = Genvoya; STB = Stribild
a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

Bone safety was assessed due to the accelerated bone loss seen in the HIV infected adult population. The initiation of ART in treatment-naive HIV infected adults is associated with a subsequent decrease in bone mineral density (BMD) in the first 12 to 24 months of use, after which BMD appears to stabilize or to effect some degree of recovery. The decrease in BMD appears to be greater with TDF than with other NtRTIs {Arribas et al 2008, McComsey et al 2011, Moyle et al 2013, Qaqish et al 2011}.

The PTs included in the Week 144 analysis of fracture events were defined by the Standardized MedDRA Query (SMQ) for osteoporosis/osteopenia and HLGT of fractures. Fracture event reported terms were clinically reviewed. The PTs included in the Week 96 analysis of fracture events were defined by the SMQ for osteoporosis/osteopenia only. Therefore, incidence of fracture between Weeks 48, 96, and 144 may differ.

Cardiovascular safety was monitored by the assessment of potential cardiovascular or cerebrovascular events. Potential cardiovascular or cerebrovascular events were defined as events with PTs in a selected PT listing provided by Gilead Sciences (Gilead) Drug Safety and Public Health and reviewed by the medical monitors. A list of PTs for potential cardiovascular or cerebrovascular findings derived from MedDRA 19.0 used in Studies GS-US-292-0104 and GS-US-292-0111, is presented in the individual study statistical analysis plans (SAPs; eg GS-US-292-0104 Week 144 SAP, Appendix 6).

Laboratory abnormalities were not usually recorded as AEs or serious AEs (SAEs). However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that required medical or surgical intervention or led to study drug interruption or discontinuation were recorded as AEs or SAEs, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiograms, x-rays, vital signs) associated with signs and/or symptoms were recorded as AEs or SAEs if they met the definitions. If the laboratory abnormality was part of a syndrome, the syndrome or diagnosis was recorded (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

All AEs and laboratory abnormalities were recorded according to uniform guidelines and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Further details of the statistical methods, safety data definitions, and grading scales are provided in GEN Integrated Summary of Safety (ISS) SAP (GEN ISS Week 144 SAP) and are included in sections below when appropriate.

Throughout the text of this document, Genvoya is referred to as “GEN.” The designation “E/C/F/TAF” is used in preprogrammed tables, figures, and listings.

### 1.1.1. Narratives of Safety Studies

Narrative safety data from Studies GS-US-292-0104 and GS-US-292-0111 are presented in m2.7.3.

## 1.2. Overall Extent of Exposure

Disposition for subjects in the GEN Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 is described in m2.7.3, Section 3.1.

### 1.2.1. Clinical Studies

Exposure to study drug for ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111 is summarized in Table 2. The duration of exposure to study drugs was similar in the 2 treatment groups. Median (first quartile [Q1], third quartile [Q3]) exposure was as follows: GEN 144.9 (143.0, 156.6) weeks; STB 144.4 (140.9, 156.4) weeks.

**Table 2. GS-US-292-0104 and GS-US-292-0111: Duration of Exposure to Study Drug (Safety Analysis Set)**

| Exposure[a,b] | GEN (N = 866) | STB (N = 867) |
|---|---|---|
| Total Exposure to Study Drug (Weeks) | | |
| N | 866 | 867 |
| Mean (SD) | 140.8 (34.31) | 137.0 (38.67) |
| Median | 144.9 | 144.4 |
| Q1, Q3 | 143.0, 156.6 | 140.9, 156.4 |
| Min, Max | 0.1, 181.1 | 0.1, 180.6 |
| Duration of Exposure to Study Drug | | |
| ≥ 4 weeks (28 days) | 859 (99.2%) | 857 (98.8%) |
| ≥ 8 weeks (56 days) | 855 (98.7%) | 854 (98.5%) |
| ≥ 12 weeks (84 days) | 853 (98.5%) | 849 (97.9%) |
| ≥ 16 weeks (112 days) | 850 (98.2%) | 844 (97.3%) |
| ≥ 24 weeks (168 days) | 842 (97.2%) | 833 (96.1%) |
| ≥ 36 weeks (252 days) | 831 (96.0%) | 821 (94.7%) |
| ≥ 48 weeks (336 days) | 827 (95.5%) | 808 (93.2%) |
| ≥ 60 weeks (420 days) | 818 (94.5%) | 795 (91.7%) |
| ≥ 72 weeks (504 days) | 808 (93.3%) | 784 (90.4%) |
| ≥ 84 weeks (588 days) | 790 (91.2%) | 770 (88.8%) |
| ≥ 96 weeks (672 days) | 779 (90.0%) | 756 (87.2%) |
| ≥ 108 weeks (756 days) | 771 (89.0%) | 749 (86.4%) |
| ≥ 120 weeks (840 days) | 763 (88.1%) | 740 (85.4%) |
| ≥ 132 weeks (924 days) | 757 (87.4%) | 727 (83.9%) |
| ≥ 144 weeks (1008 days) | 578 (66.7%) | 551 (63.6%) |
| ≥ 156 weeks (1092 days) | 327 (37.8%) | 299 (34.5%) |
| ≥ 168 weeks (1176 days) | 105 (12.1%) | 115 (13.3%) |
| ≥ 180 weeks (1260 days) | 5 (0.6%) | 4 (0.5%) |

a Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.
b If the last dose date was completely missing, or only the year was known, or a subject was still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day Follow-up Visit date) was used to impute the last dose date; if the last study drug end date was nonmissing, then it was used to impute the last dose date.

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Source: GEN Week 144 ISS, Table 4

### 1.2.2. Postmarketing Data

Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents 12 years and above in the United States (US) on 05 November 2015 and in the European Union on 19 November 2015. As of 21 July 2016, cumulative patient exposure to GEN is estimated to be 30,743 patient-years. This estimate is based on sales data, which generally overestimates patient exposure because stocks of drug are accumulated by distributors and pharmacies.

## 1.3. Summary of Demographic and General Baseline Characteristics

### 1.3.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics for the pooled Safety Analysis Set in ART-naive adults in Studies GS-US-292-0104 and GS-US-292-0111 were similar in the 2 treatment groups (Table 3). The majority of subjects were male (85.0%). The median age was as follows: GEN 33 years (range: 18 to 74); STB 35 years (range: 18 to 76). Subjects were most commonly white (56.7%), black (25.2%), or Asian (10.4%), and most subjects were not of Hispanic or Latino ethnicity (80.6%). The median (Q1, Q3) value for body mass index at baseline was 24.5 (21.8, 28.0) kg/m².

**Table 3. GS-US-292-0104 and GS-US-292-0111: Demographics and Baseline Characteristics (Safety Analysis Set)**

| Characteristic[a] | GEN (N = 866) | STB (N = 867) | Total (N = 1733) |
|---|---|---|---|
| Age (Years) | | | |
| N | 866 | 867 | 1733 |
| Mean (SD) | 35 (10.4) | 36 (10.7) | 36 (10.6) |
| Median | 33 | 35 | 34 |
| Q1, Q3 | 26, 42 | 28, 44 | 27, 43 |
| Min, Max | 18, 74 | 18, 76 | 18, 76 |
| Sex | | | |
| Male | 733 (84.6%) | 740 (85.4%) | 1473 (85.0%) |
| Female | 133 (15.4%) | 127 (14.6%) | 260 (15.0%) |
| Race | | | |
| American Indian or Alaska Native | 5 (0.6%) | 8 (0.9%) | 13 (0.8%) |
| Asian | 91 (10.5%) | 89 (10.3%) | 180 (10.4%) |
| Black | 223 (25.8%) | 213 (24.6%) | 436 (25.2%) |
| Native Hawaiian or Pacific Islander | 5 (0.6%) | 4 (0.5%) | 9 (0.5%) |
| White | 485 (56.0%) | 498 (57.4%) | 983 (56.7%) |
| Other | 57 (6.6%) | 55 (6.3%) | 112 (6.5%) |

| Characteristic[a] | GEN (N = 866) | STB (N = 867) | Total (N = 1733) |
|---|---|---|---|
| Ethnicity | | | |
| Hispanic or Latino | 167 (19.3%) | 167 (19.3%) | 334 (19.3%) |
| Not Hispanic or Latino | 698 (80.6%) | 698 (80.6%) | 1396 (80.6%) |
| Not Permitted[b] | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Missing | 0 | 1 | 1 |
| Region | | | |
| US | 532 (61.4%) | 532 (61.4%) | 1064 (61.4%) |
| ex-US | 334 (38.6%) | 335 (38.6%) | 669 (38.6%) |
| Baseline Body Mass Index ($kg/m^2$) | | | |
| N | 866 | 867 | 1733 |
| Mean (SD) | 25.5 (5.23) | 25.5 (5.12) | 25.5 (5.17) |
| Median | 24.4 | 24.5 | 24.5 |
| Q1, Q3 | 22.0, 28.0 | 21.7, 28.0 | 21.8, 28.0 |
| Min, Max | 16.6, 71.0 | 16.6, 54.3 | 16.6, 71.0 |

a The denominator for percentages is the number of subjects in the Safety Analysis Set.
b Not permitted = Regulators do not allow collection of ethnicity information.
Programming Details: .../version1/prog/t-demog.sas v9.2 09AUG2016:12:05
Source: GEN Week 144 ISS, Table 2

### 1.3.2. Baseline Disease Characteristics

Baseline disease characteristics for ART-naive adult subjects in the pooled Studies GS-US-292-0104 and GS-US-292-0111 Safety Analysis Set are summarized in Table 4, and were generally similar in the 2 treatment groups.

Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.58 (4.14, 4.96) $\log_{10}$ copies/mL. At baseline, 77.4% of subjects had HIV-1 RNA ≤ 100,000 copies/mL, 17.4% had HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL, and 5.2% had HIV-1 RNA > 400,000 copies/mL. Overall, the median (Q1, Q3) baseline CD4 cell count was 405 (288, 548) cells/µL; 2.9% of subjects had a CD4 cell count < 50 cells/µL and 10.3% had a CD4 cell count ≥ 50 to < 200 cells/µL. The most common HIV risk factor category was homosexual sex (74.8% of subjects); heterosexual sex was reported as the mode of infection for 24.8% of subjects. The majority of subjects (91.5%) had asymptomatic HIV-1 infection; 5.0% had symptomatic HIV-1 infection, and 3.5% were diagnosed with AIDS.

The median (Q1, Q3) baseline value for eGFR calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) was 115.6 (99.5, 134.4) mL/min. Overall, 174 subjects (10.0%) had proteinuria (Grade 1, 2, or 3) by dipstick at baseline.

Overall, the medical history of subjects was as follows: hypertension (15.5%), hyperlipidemia (13.4%), diabetes (3.8%), and cardiovascular disease (1.4%).

**Table 4. GS-US-292-0104 and GS-US-292-0111: Baseline Disease Characteristics (Safety Analysis Set)**

| Characteristic[a] | GEN (N = 866) | STB (N = 867) | Total (N = 1733) |
|---|---|---|---|
| HIV-1 RNA ($log_{10}$ copies/mL) | | | |
| N | 866 | 867 | 1733 |
| Mean (SD) | 4.54 (0.665) | 4.53 (0.682) | 4.53 (0.673) |
| Median | 4.58 | 4.58 | 4.58 |
| Q1, Q3 | 4.14, 4.95 | 4.15, 4.96 | 4.14, 4.96 |
| Min, Max | 2.57, 6.89 | 1.28, 6.98 | 1.28, 6.98 |
| HIV-1 RNA category (copies/mL) | | | |
| ≤ 100,000 | 670 (77.4%) | 672 (77.5%) | 1342 (77.4%) |
| > 100,000 to ≤ 400,000 | 147 (17.0%) | 154 (17.8%) | 301 (17.4%) |
| > 400,000 | 49 (5.7%) | 41 (4.7%) | 90 (5.2%) |
| CD4 cell count (/μL) | | | |
| N | 865 | 867 | 1732 |
| Mean (SD) | 426 (215.6) | 429 (219.6) | 427 (217.5) |
| Median | 404 | 406 | 405 |
| Q1, Q3 | 283, 550 | 291, 542 | 288, 548 |
| Min, Max | 0, 1311 | 1, 1360 | 0, 1360 |
| CD4 cell count category (/μL) | | | |
| < 50 | 24 (2.8%) | 27 (3.1%) | 51 (2.9%) |
| ≥ 50 to < 200 | 88 (10.2%) | 90 (10.4%) | 178 (10.3%) |
| ≥ 200 to < 350 | 218 (25.2%) | 200 (23.1%) | 418 (24.1%) |
| ≥ 350 to < 500 | 256 (29.6%) | 284 (32.8%) | 540 (31.2%) |
| ≥ 500 | 279 (32.3%) | 266 (30.7%) | 545 (31.5%) |
| Missing | 1 | 0 | 1 |
| Mode of infection (HIV risk factors) (n, %)[b] | | | |
| Heterosexual sex | 210 (24.2%) | 219 (25.3%) | 429 (24.8%) |
| Homosexual sex | 652 (75.3%) | 645 (74.4%) | 1297 (74.8%) |
| IV drug use | 5 (0.6%) | 6 (0.7%) | 11 (0.6%) |
| Transfusion | 2 (0.2%) | 6 (0.7%) | 8 (0.5%) |
| Vertical transmission | 2 (0.2%) | 0 | 2 (0.1%) |
| Unknown | 18 (2.1%) | 27 (3.1%) | 45 (2.6%) |
| Other | 18 (2.1%) | 9 (1.0%) | 27 (1.6%) |

| Characteristic[a] | GEN (N = 866) | STB (N = 867) | Total (N = 1733) |
|---|---|---|---|
| HIV disease status (n, %) | | | |
| Asymptomatic | 779 (90.3%) | 800 (92.7%) | 1579 (91.5%) |
| Symptomatic HIV infection | 53 (6.1%) | 34 (3.9%) | 87 (5.0%) |
| AIDS | 31 (3.6%) | 29 (3.4%) | 60 (3.5%) |
| Unknown | 3 | 4 | 7 |
| $eGFR_{CG}$ (mL/min) | | | |
| N | 866 | 867 | 1733 |
| Mean (SD) | 120.8 (30.87) | 118.7 (30.73) | 119.7 (30.81) |
| Median | 117.0 | 113.9 | 115.6 |
| Q1, Q3 | 99.6, 135.6 | 99.0, 133.6 | 99.5, 134.4 |
| Min, Max | 33.7, 287.2 | 55.3, 320.2 | 33.7, 320.2 |
| Proteinuria by urinalysis (n, %) | | | |
| Grade 0 | 778 (89.8%) | 780 (90.1%) | 1558 (90.0%) |
| Grade 1 | 80 (9.2%) | 67 (7.7%) | 147 (8.5%) |
| Grade 2 | 8 (0.9%) | 18 (2.1%) | 26 (1.5%) |
| Grade 3 | 0 | 1 (0.1%) | 1 (< 0.1%) |
| Missing | 0 | 1 | 1 |
| Diabetes mellitus (n, %)[c] | | | |
| Yes | 25 (2.9%) | 40 (4.6%) | 65 (3.8%) |
| No | 841 (97.1%) | 827 (95.4%) | 1668 (96.2%) |
| Hypertension (n, %)[c] | | | |
| Yes | 120 (13.9%) | 148 (17.1%) | 268 (15.5%) |
| No | 746 (86.1%) | 719 (82.9%) | 1465 (84.5%) |
| Cardiovascular disease (n, %)[c] | | | |
| Yes | 10 (1.2%) | 14 (1.6%) | 24 (1.4%) |
| No | 856 (98.8%) | 853 (98.4%) | 1709 (98.6%) |
| Hyperlipidemia (n, %)[c] | | | |
| Yes | 118 (13.6%) | 114 (13.1%) | 232 (13.4%) |
| No | 748 (86.4%) | 753 (86.9%) | 1501 (86.6%) |

a The denominator for percentages is the number of subjects in the Safety Analysis Set.
b A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
c Medical history characteristics (diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia) were determined by past medical history.

Programming Details: .../version1/prog/t-basechar.sas v9.2 09AUG2016:12:02
Source: GEN Week 144 ISS, Table 3

# 2. ADVERSE EVENTS

## 2.1. Analysis of Adverse Events

For the category of AE leading to premature study drugs discontinuation, fewer subjects in the GEN group had AEs that resulted in discontinuation of study drugs compared with subjects in the STB group, as follows: GEN 1.3%, 11 of 866 subjects; STB 3.3%, 29 of 867 subjects. The difference was driven primarily by study drugs discontinuation due to bone and renal events in the STB group, as follows: GEN 0 subjects; STB 17 subjects (of which 1 subject had both bone and renal events; GEN Week 144 ISS, Listing 3). The percentage of subjects that had any AE considered related to study drugs by the investigator was lower in the GEN group compared with the STB group, as follows: GEN 44.1%, 382 subjects; STB 48.9%, 424 subjects. For other categories, similar percentages of subjects in each treatment group were reported (Table 5).

**Table 5. Studies GS-US-292-0104 and GS-US-292-0111: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)**

| | GEN (N=866) | STB (N=867) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 817 (94.3%) | 833 (96.1%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 559 (64.5%) | 552 (63.7%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 140 (16.2%) | 137 (15.8%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 382 (44.1%) | 424 (48.9%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 109 (12.6%) | 113 (13.0%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 15 (1.7%) | 15 (1.7%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 121 (14.0%) | 124 (14.3%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 5 (0.6%) | 6 (0.7%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 11 (1.3%) | 29 (3.3%) |
| Subjects who had Treatment-Emergent Death | 4 (0.5%) | 5 (0.6%) |

Programming Details: .../version1/prog/t-ae.sas v9.2 Output file: t-aebrief.out 09AUG2016:12:01
Source: GEN Week 144 ISS, Table 6

### 2.1.1. Common Adverse Events

Pooled results for Studies GS-US-292-0104 and GS-US-292-0111 are described below; AEs that occurred in ≥ 10% of subjects in either treatment group during the studies are presented in Table 6. The 3 most commonly reported AEs by treatment group were as follows:

- GEN — diarrhea (23.4%, 203 of 866 subjects), upper respiratory tract infection (20.3%, 176 subjects), and headache (19.2%, 166 subjects)
- STB — diarrhea (24.5%, 212 of 867 subjects), upper respiratory tract infection (19.6%, 170 subjects), and nausea (19.3%, 167 subjects)

The rates and types of common AEs were similar in the 2 treatment groups and consistent with those expected in the study population. No AE was reported with a ≥ 5% difference in incidence between treatment groups.

**Table 6. GS-US-292-0104 and GS-US-292-0111: Adverse Events Reported for ≥ 10% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | GEN (N=866) | STB (N=867) |
|---|---|---|
| Number of Subjects Experiencing Any Treatment-Emergent Adverse Event | 817 (94.3%) | 833 (96.1%) |
| Gastrointestinal disorders | 508 (58.7%) | 521 (60.1%) |
| Diarrhea | 203 (23.4%) | 212 (24.5%) |
| Nausea | 150 (17.3%) | 167 (19.3%) |
| General disorders and administration site conditions | 256 (29.6%) | 231 (26.6%) |
| Fatigue | 101 (11.7%) | 97 (11.2%) |
| Infections and infestations | 661 (76.3%) | 650 (75.0%) |
| Upper respiratory tract infection | 176 (20.3%) | 170 (19.6%) |
| Nasopharyngitis | 125 (14.4%) | 123 (14.2%) |
| Syphilis | 86 (9.9%) | 97 (11.2%) |
| Musculoskeletal and connective tissue disorders | 364 (42.0%) | 365 (42.1%) |
| Back pain | 104 (12.0%) | 104 (12.0%) |
| Arthralgia | 104 (12.0%) | 82 (9.5%) |
| Osteopenia | 69 (8.0%) | 87 (10.0%) |
| Nervous system disorders | 286 (33.0%) | 270 (31.1%) |
| Headache | 166 (19.2%) | 135 (15.6%) |
| Psychiatric disorders | 260 (30.0%) | 262 (30.2%) |
| Insomnia | 94 (10.9%) | 68 (7.8%) |

| Adverse Events by System Organ Class and Preferred Term | GEN (N=866) | STB (N=867) |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 266 (30.7%) | 264 (30.4%) |
| Cough | 117 (13.5%) | 102 (11.8%) |

Adverse events were coded using MedDRA 19.0.
System organ class (SOC) and high level term (within each SOC) were presented alphabetically, and preferred term was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class, high level term, and preferred term, respectively.
Programming Details: .../version1/prog/t-ae.sas v9.2 09AUG2016:12:01
Source: GEN Week 144 ISS, Table 7

### Adverse Events by Severity

The majority of AEs reported in Studies GS-US-292-0104 and GS-US-292-0111 were Grade 1 or 2 (GEN Week 144 ISS, Table 6). Similar percentages of subjects in each treatment group had any Grade 3 or 4 AE (GEN 16.2%, 140 subjects; STB 15.8%, 137 subjects) (GEN Week 144 ISS, Table 10).

No individual Grade 3 or 4 AEs were reported for ≥ 1% of subjects in either treatment group.

### Adverse Events Considered Related to Study Drug

The percentage of subjects that had any AE considered related to study drugs by the investigator was lower in the GEN group compared with the STB group, as follows: GEN 44.1%, 382 of 866 subjects; STB 48.9%, 424 of 867 subjects (Table 7). The 3 most commonly reported AEs considered related to study drug by the investigator by treatment group were as follows:

- GEN — nausea (10.5%, 91 subjects), diarrhea (7.3%, 63 subjects), and headache (6.1%, 53 subjects)
- STB — nausea (13.3%, 115 subjects), diarrhea (8.9%, 77 subjects), and headache (5.4%, 47 subjects)

**Table 7. GS-US-292-0104 and GS-US-292-0111: Adverse Events Related to Study Drug Reported for ≥ 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | GEN (N=866) | STB (N=867) |
|---|---|---|
| Number of Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 382 ( 44.1%) | 424 ( 48.9%) |
| Nausea | 91 ( 10.5%) | 115 ( 13.3%) |
| Diarrhea | 63 ( 7.3%) | 77 ( 8.9%) |
| Flatulence | 23 ( 2.7%) | 29 ( 3.3%) |
| Vomiting | 16 ( 1.8%) | 29 ( 3.3%) |
| Abdominal pain | 12 ( 1.4%) | 11 ( 1.3%) |
| Abdominal pain upper | 11 ( 1.3%) | 12 ( 1.4%) |
| Abdominal distension | 12 ( 1.4%) | 9 ( 1.0%) |
| Fatigue | 44 ( 5.1%) | 38 ( 4.4%) |
| Bone density decreased | 8 ( 0.9%) | 11 ( 1.3%) |
| Decreased appetite | 13 ( 1.5%) | 8 ( 0.9%) |
| Osteopenia | 32 ( 3.7%) | 40 ( 4.6%) |
| Osteoporosis | 8 ( 0.9%) | 12 ( 1.4%) |
| Headache | 53 ( 6.1%) | 47 ( 5.4%) |
| Dizziness | 26 ( 3.0%) | 20 ( 2.3%) |
| Somnolence | 9 ( 1.0%) | 10 ( 1.2%) |
| Abnormal dreams | 13 ( 1.5%) | 29 ( 3.3%) |
| Insomnia | 18 ( 2.1%) | 15 ( 1.7%) |
| Proteinuria | 8 ( 0.9%) | 22 ( 2.5%) |
| Rash | 15 ( 1.7%) | 9 ( 1.0%) |

Adverse events were coded using MedDRA 19.0.
System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Programming Details: .../version1/prog/t-ae.sas v9.2 Output file: t-aerel.out 09AUG2016:12:01
Source: GEN Week 144 ISS, Table 11

### 2.1.2. Deaths

Nine treatment-emergent deaths were reported through Week 144 (GEN 4 subjects: completed suicide, cerebral infarction, cerebrovascular accident, and alcohol poisoning [1 subject each]; STB 5 subjects: cardiac arrest [2 subjects], unknown cause and acute myocardial infarction [1 subject each]; recreational drug and alcohol overdose [both in 1 subject]) in Studies GS-US-292-0104 and GS-US-292-0111 (GEN Week 144 ISS, Listing 4). Two additional deaths were reported through Week 144 that were not treatment emergent as they occurred more

than 30 days after the last dose of study drugs (GEN 1 subject: myocardial infarction; STB 1 subject: non-small cell lung cancer). All SAEs that resulted in death were considered not related to study drug by the investigator (GEN Week 144 ISS, Listing 1).

Further details of these deaths are provided in the individual study clinical study reports (CSRs) (GS-US-292-0104 Week 144, Section 11.3; GS-US-292-0111 Week 144, Section 11.3).

### 2.1.3. Other Serious Adverse Events

Serious AEs were reported for similar percentages of subjects in each treatment group in Studies GS-US-292-0104 and GS-US-292-0111 (GEN 14.0%, 121 of 866 subjects; STB 14.3%, 124 of 867 subjects) (GEN Week 144 ISS, Table 6). Overall, the incidence of SAEs considered related to study drugs by the investigator was low and similar in each treatment group (GEN 0.6%, 5 subjects; STB 0.7%, 6 subjects).

Appendicitis was the only SAE that occurred in ≥ 1% of subjects in either treatment group (GEN 1.0%, 9 subjects; STB 0.8%, 7 subjects) (GEN Week 144 ISS, Tables 14 and 15). None of the appendicitis SAEs were considered related to study drugs by the investigator.

No SAE considered related to study drugs by the investigator was reported for > 1 subject in either treatment group (GEN Week 144 ISS, Table 15).

Six subjects had SAEs due to renal and urinary disorder or associated investigation (GEN 3 subjects: ureterolithiasis, nephrotic syndrome, and postinfectious glomerulonephritis; STB 3 subjects: ureterolithiasis, acute kidney infection, and renal hematoma); these events are described in Section 2.1.5.2.1.

### 2.1.4. Other Significant Adverse Events

The incidence of AEs leading to discontinuation of study drugs in Studies GS-US-292-0104 and GS-US-292-0111 was lower in the GEN group compared with the STB group, as follows: GEN 1.3%, 11 of 866 subjects; STB 3.3%, 29 of 867 subjects (GEN Week 144 ISS, Table 16). The difference was driven primarily by study drugs discontinuation due to bone and renal events in the STB group. In the GEN group, no subjects had bone or renal events that resulted in discontinuation of study drugs; however, in the STB group, 6 subjects had bone events (Section 2.1.5.1.2) and 12 subjects had renal events (Section 2.1.5.2.1) that resulted in discontinuation of study drugs. One subject in the STB group had both bone and renal events.

Overall, most AEs leading to discontinuation of study drug were nonserious and considered related to study drugs by the investigator. No AE leading to discontinuation was reported for > 1 subject in the GEN group. Six AEs leading to discontinuation were reported for > 1 subject in the STB group (bone density decreased and renal tubular disorder [0.3%, 3 subjects each]; vomiting, blood creatinine increased, glomerular filtration rate decreased, headache, and renal failure [0.2%, 2 subjects each]) (GEN Week 144 ISS, Table 16).

## 2.1.5. Analysis of Adverse Events by Organ System or Syndrome

### 2.1.5.1. Bone Safety

Bone safety is described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 144, Section 11.2.4.1; GS-US-292-0111 Week 144, Section 11.2.4.1).

#### 2.1.5.1.1. Fracture Events

In Studies GS-US-292-0104 and GS-US-292-0111, the incidence of fracture events (as defined by the SMQ for osteoporosis/osteopenia and fractures HLGT) was similar in both treatment groups (GEN 3.6%, 31 of 866 subjects; STB 4.5%, 39 of 867 subjects; GEN Week 144 ISS, Table 25). Fracture AEs were reported as serious for 6 subjects in the GEN group (ankle fracture [2 subjects]; femur fracture, foot fracture, humerus fracture, and lower limb fracture [1 subject each]) and 6 subjects in the STB group (ankle fracture, thoracic vertebral fracture, cervical vertebral fracture, facial bones fracture, and radius fracture [1 subject each]; and thoracic vertebral fracture, rib fracture, and ulna fracture [all in 1 subject]) (Week 144 GEN ISS, Table 14 and Listing 1). No fracture AE was considered by the investigator as related to study drug or resulted in discontinuation of study drug.

#### 2.1.5.1.2. Bone Events

No subject in Studies GS-US-292-0104 and GS-US-292-0111 discontinued GEN due to a bone AE; however, 6 subjects discontinued STB due to bone AEs: bone density decreased (3 subjects); and bone loss, osteopenia, and osteoporosis (1 subject each) (GEN Week 144 ISS, Table 16 and Listing 3).

The incidence of AEs related to BMD (AEs reported as bone loss or bone mineral decreased) were as follows: GEN 1.3%, 11 subjects; STB 1.7%, 15 subjects (GEN Week 144 ISS, Tables 7, 11, 14, and 16). The incidences of bone loss reported as an AE were as follows: GEN 0.1%, 1 subject; STB 0.2%, 2 subjects. All bone loss AEs were nonserious. Bone loss AEs were considered related to study drugs by the investigator for 2 subjects, both in the STB group. The incidences of bone density decreased reported as AEs were as follows: GEN 1.2%, 10 subjects; STB: 1.5%, 13 subjects. All bone density decreased AEs were nonserious. Bone density decreased AEs were considered related to study drugs by the investigator for the following: GEN 0.9%, 8 subjects; STB 1.3%, 11 subjects.

The incidences of osteopenia and osteoporosis reported as an AE were as follows: osteopenia: GEN 8.0%, 69 subjects; STB 10.0%, 87 subjects; osteoporosis: GEN 2.0%, 17 subjects; STB 2.9%, 25 subjects (GEN Week 144 ISS, Tables 7, 11, 14, and 16). Osteopenia was considered related to study drugs for 72 subjects: GEN 32 subjects (3.7%); STB 40 subjects (4.6%). Osteoporosis was considered related to study drugs for 20 subjects: GEN 8 subjects (0.9%); STB 12 subjects (1.4%). All AEs of osteopenia or osteoporosis were nonserious.

#### 2.1.5.1.3. Percentage Change from Baseline in Hip and Spine BMD

For both hip and spine BMD, the difference between treatment groups in the percentage change from baseline was statistically significant ($p < 0.001$) at all visits. Mean percentage decreases from baseline in hip and spine BMD at Week 144 were smaller in the GEN group than the STB group in Studies GS-US-292-0104 and GS-US-292-0111 (Figure 1 and Figure 2, respectively; GEN Week 144 ISS, Tables 20.1.2 and 20.2.2).

Mean (SD) baseline hip BMD values were similar in each treatment group (GEN 1.041 [0.1557] g/cm$^2$; STB 1.028 [0.1480] g/cm$^2$); mean (SD) decreases from baseline at Week 144 were as follows:

- GEN 0.750% (4.4478%)
- STB 3.364% (4.3292%)

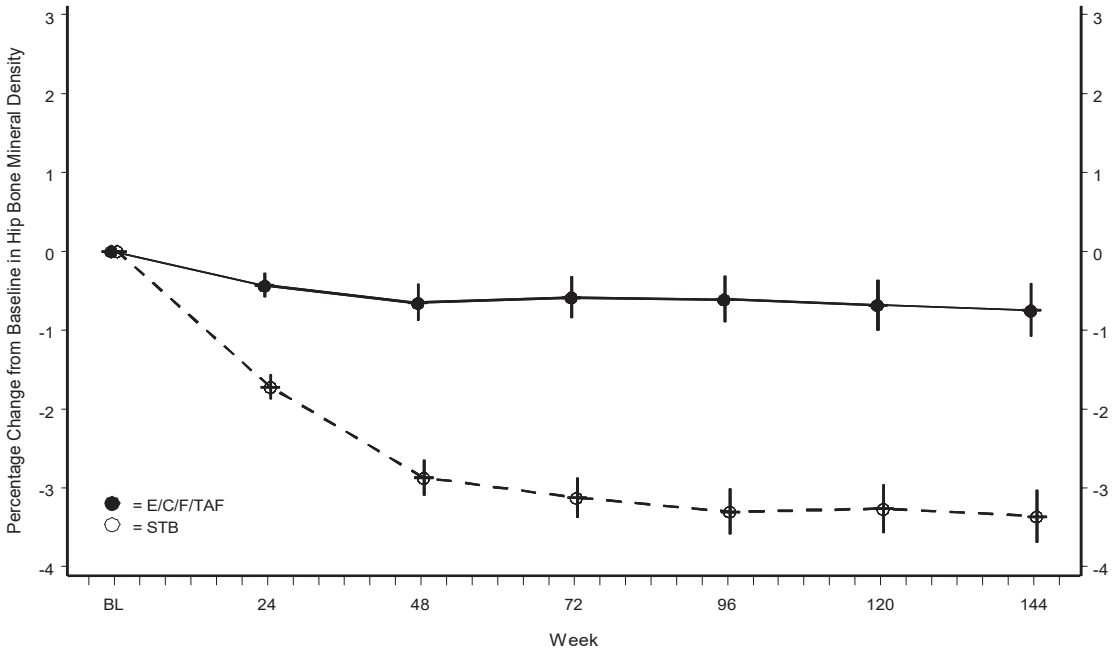
Mean (SD) baseline spine BMD was higher in the GEN group than the STB group (GEN 1.135 [0.1758] g/cm$^2$; STB 1.114 [0.1623] g/cm$^2$; $p = 0.011$); mean (SD) decreases from baseline at Week 144 were as follows:

- GEN 0.916% (4.1186%)
- STB 2.952% (4.2938%)

Analysis using the last observation carried forward (LOCF) method to replace missing values showed similar results to the observed data (GEN Week 144 ISS, Tables 20.1.1 and 20.2.1).

Sensitivity analyses of percentage changes from baseline in BMD at the hip and spine were performed to exclude subjects who took osteoporosis medications at study entry or initiated osteoporosis medications during the study. The results of this analysis were consistent with those observed for all subjects in the Hip and Spine DXA Analysis Sets (GEN Week 144 ISS, Tables 21.2.1 and 21.2.2).

**Figure 1. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Hip BMD by Visit (Observed Data; Hip DXA Analysis Set)**



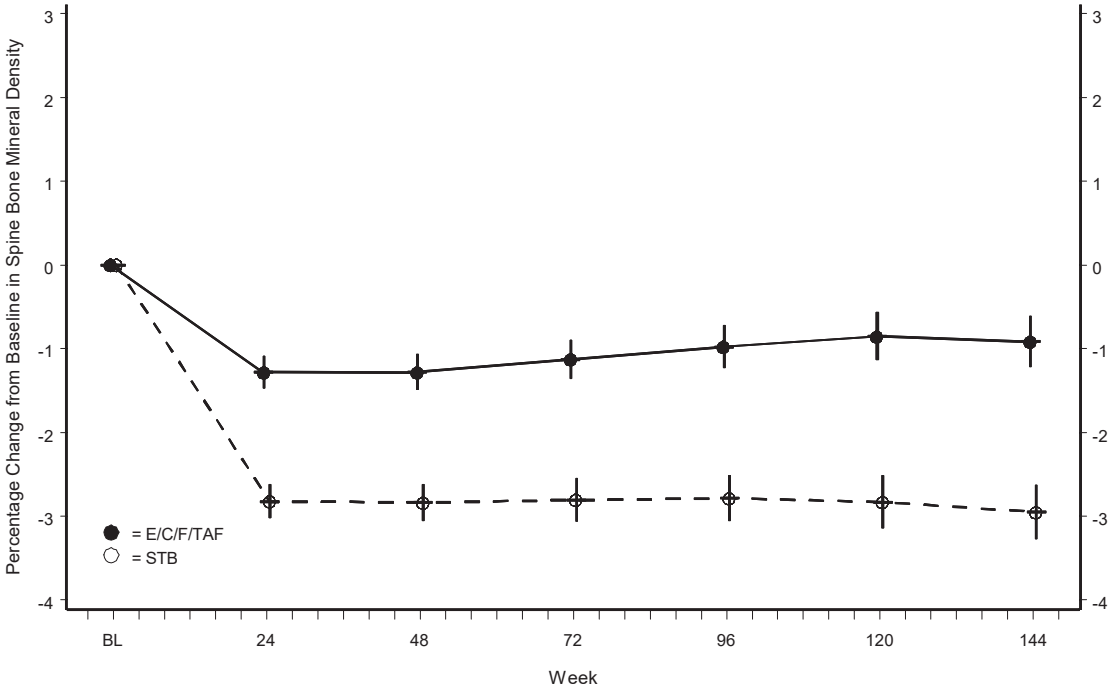

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 836 | 789 | 791 | 751 | 735 | 699 | 690 |
| STB (n=): | 848 | 815 | 784 | 741 | 742 | 705 | 683 |

BL = Baseline.
Only subjects with nonmissing hip BMD for the baseline visit were included in hip DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: 22JUL2016, Lab Data: 25JUL2016, s292-0111: CRF Data: 28JUL2016, Lab Data: 29JUL2016, DXA Data: 26JUL2016
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-hip-bmd-mn.out 09AUG2016:12:06

Source: GEN Week 144 ISS, Figure 3.2.1

**Figure 2. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 845 | 797 | 795 | 760 | 744 | 706 | 702 |
| STB (n=): | 850 | 816 | 790 | 751 | 745 | 707 | 686 |

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: 22JUL2016, Lab Data: 25JUL2016, s292-0111: CRF Data: 28JUL2016, Lab Data: 29JUL2016, DXA Data: 26JUL2016
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out 09AUG2016:12:06

Source: GEN Week 144 ISS, Figure 3.2.2

## Categorical Distribution of Percentage Change from Baseline in BMD

Differences between treatment groups in the categorical distribution of percentage change from baseline in hip and spine BMD were statistically significant ($p < 0.001$) at Weeks 24, 48, 72, 96, and 144 (GEN Week 144 ISS, Tables 23.1 and 23.2, respectively).

At Week 144, fewer subjects in the GEN group than the STB group had decreases from baseline in hip and spine BMD, and more subjects in the GEN group than the STB group had a > 3% increase from baseline in hip and spine BMD (Table 8). The percentages of subjects with a > 3% decrease from baseline in BMD at Week 144 were as follows:

- Hip BMD: GEN 28.0%, STB 55.5%
- Spine BMD: GEN 30.2%, STB 49.0%

The percentages of subjects with a > 3% increase from baseline in BMD at Week 144 were as follows:

- Hip BMD: GEN 13.2%, STB 6.3%
- Spine BMD: GEN 13.4%, STB 6.9%

**Table 8. GS-US-292-0104 and GS-US-292-0111: Categorical Distribution of Changes in Hip and Spine BMD at Weeks 48, 96, and 144 (Hip and Spine DXA Analysis Sets)**

| | GEN n/N (%) | STB n/N (%) |
|---|---|---|
| **Changes in Hip BMD[a]** | | |
| Percentage Change at Week 48 | | |
| > 7% Decrease | 16/791 (2.0%) | 58/784 (7.4%) |
| > 3% Decrease | 133/791 (16.8%) | 392/784 (50.0%) |
| No Decrease (≥ 0% Change) | 280/791 (35.4%) | 109/784 (13.9%) |
| > 3% Increase | 53/791 (6.7%) | 28/784 (3.6%) |
| Percentage Change at Week 96 | | |
| > 7% Decrease | 23/735 (3.1%) | 100/742 (13.5%) |
| > 3% Decrease | 170/735 (23.1%) | 420/742 (56.6%) |
| No Decrease (≥ 0% Change) | 285/735 (38.8%) | 116/742 (15.6%) |
| > 3% Increase | 90/735 (12.2%) | 40/742 (5.4%) |
| Percentage Change at Week 144 | | |
| > 7% Decrease | 29/690 (4.2%) | 115/683 (16.8%) |
| > 3% Decrease | 193/690 (28.0%) | 379/683 (55.5%) |
| No Decrease (≥ 0% Change) | 275/690 (39.9%) | 128/683 (18.7%) |
| > 3% Increase | 91/690 (13.2%) | 43/683 (6.3%) |
| **Changes in Spine BMD[b]** | | |
| Percentage Change at Week 48 | | |
| > 5% Decrease | 79/795 (9.9%) | 183/790 (23.2%) |
| > 3% Decrease | 216/795 (27.2%) | 365/790 (46.2%) |
| No Decrease (≥ 0% Change) | 272/795 (34.2%) | 135/790 (17.1%) |
| > 3% Increase | 53/795 (6.7%) | 22/790 (2.8%) |
| Percentage Change at Week 96 | | |
| > 5% Decrease | 87/744 (11.7%) | 187/745 (25.1%) |
| > 3% Decrease | 200/744 (26.9%) | 359/745 (48.2%) |
| No Decrease (≥ 0% Change) | 276/744 (37.1%) | 156/745 (20.9%) |
| > 3% Increase | 81/744 (10.9%) | 43/745 (5.8%) |

| | GEN n/N (%) | STB n/N (%) |
|---|---|---|
| Percentage Change at Week 144 | | |
| > 5% Decrease | 103/702 (14.7%) | 199/686 (29.0%) |
| > 3% Decrease | 212/702 (30.2%) | 336/686 (49.0%) |
| No Decrease (≥ 0% Change) | 273/702 (38.9%) | 149/686 (21.7%) |
| > 3% Increase | 94/702 (13.4%) | 47/686 (6.9%) |

a Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.
b Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.
Source: GEN Week 144 ISS, Tables 23.1 and 23.2

#### 2.1.5.1.4. Bone Laboratory Parameters

Changes from baseline in parathyroid hormone, a hormone involved in bone metabolism, were smaller in the GEN group than the STB group at Weeks 48, 96, and 144 ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline) (GEN Week 144 ISS, Table 24).

Median (Q1, Q3) percentage changes from baseline at Week 144 were as follows: GEN 47.3% (15.5%, 102.1%), STB 71.8% (33.2%, 124.5%).

Changes in C-telopeptide (bone resorption) and procollagen type 1 N-terminal propeptide (bone formation) were only assessed through Week 96.

### 2.1.5.2. Renal Safety

Renal safety is described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 144, Section 11.2.4.2; GS-US-292-0111 Week 144, Section 11.2.4.2).

#### 2.1.5.2.1. Renal Events

No subjects in Studies GS-US-292-0104 and GS-US-292-0111 discontinued GEN due to a renal and urinary disorder or associated investigation AE, compared with 12 subjects who discontinued STB (1.4%; $p < 0.001$; Table 9). Discontinuations of study drugs due to renal and urinary disorder or associated investigation AEs that are indicative of proximal renal tubulopathy in the STB group were reported for 4 subjects, as follows: renal tubular disorder, 3 subjects (1 subject had a renal tubular disorder reported as injury level renal tubule, 2 subjects had proteinuria, normoglycemic glycosuria, and elevated serum creatinine in addition to renal tubular disorder); and acquired Fanconi syndrome, 1 subject (this subject also had proteinuria, elevated serum creatinine, hypophosphatemia, and a concurrent AE of glycosuria). All but 1 of 14 renal and urinary disorders or associated investigation events (blood creatinine increased) that led to discontinuation of STB were considered related to study drug by the investigator. The subject who had an AE of blood creatinine increased that was not considered related to study drugs by the investigator also had an AE of bone density decreased (GEN Week 144 ISS, Listing 3).

Serious AEs due to renal and urinary disorder or associated investigation were reported as follows: GEN 3 subjects (Grade 3: ureterolithiasis and postinfectious glomerulonephritis; Grade 2: nephrotic syndrome [1 subject each]); STB 3 subjects (Grade 3: renal hematoma; Grade 2: ureterolithiasis and acute kidney infection [1 subject each]) (GEN Week 144 ISS, Table 14 and Listing 1). None of the renal SAEs were indicative of proximal renal tubulopathy or considered related to study drugs by the investigator, and none resulted in the discontinuation of study drugs. Each renal SAE resolved without interruption to study drugs.

**Table 9. GS-US-292-0104 and GS-US-292-0111: Treatment-Emergent Renal Adverse Events Leading to Premature Study Drug Discontinuation (Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | GEN (N = 866) | STB (n = 867) | p-value[a] |
|---|---|---|---|
| Number of Subjects Experiencing Any Treatment-Emergent Renal Adverse Event Leading to Premature Study Drug Discontinuation | 0 | 12 (1.4%) | <0.001 |
| Investigations | 0 | 3 (0.3%) | |
| Blood creatinine increased | 0 | 2 (0.2%) | |
| Glomerular filtration rate decreased | 0 | 2 (0.2%) | |
| Renal and urinary disorders | 0 | 9 (1.0%) | |
| Renal tubular disorder | 0 | 3 (0.3%) | |
| Renal failure | 0 | 2 (0.2%) | |
| Bladder spasm[b] | 0 | 1 (0.1%) | |
| Fanconi syndrome acquired | 0 | 1 (0.1%) | |
| Glycosuria | 0 | 1 (0.1%) | |
| Nephropathy | 0 | 1 (0.1%) | |
| Proteinuria | 0 | 1 (0.1%) | |

a P-value was from the Fisher's exact test.
b The AE of bladder spasm was not considered to be an intrinsic kidney disorder.
Adverse events were coded using MedDRA 19.0.
System organ class (SOC) was presented alphabetically and preferred term was presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and preferred term (PT), respectively.
Renal adverse events included SOC="Renal and urinary disorders" or PT="Blood creatinine increased" or PT="Glomerular filtration rate decreased".
Source: GEN Week 144 ISS, Table req8462.1

### 2.1.5.2.2. Renal Laboratory Parameters

#### 2.1.5.2.2.1. Serum Creatinine

The difference between treatment groups in change from baseline in serum creatinine was statistically significant at all but 1 time point from Weeks 2 through 144 ($p < 0.001$ except at Week 108). Overall, increases from baseline in mean values for serum creatinine were smaller in the GEN group compared with the STB group (Figure 3). Increases were observed by Week 2 in

both treatment groups, and remained evident through Week 144. Mean (SD) baseline serum creatinine values were as follows: GEN 0.93 (0.172) mg/dL; STB 0.94 (0.169) mg/dL (GEN Week 144 ISS, Table 26.2).

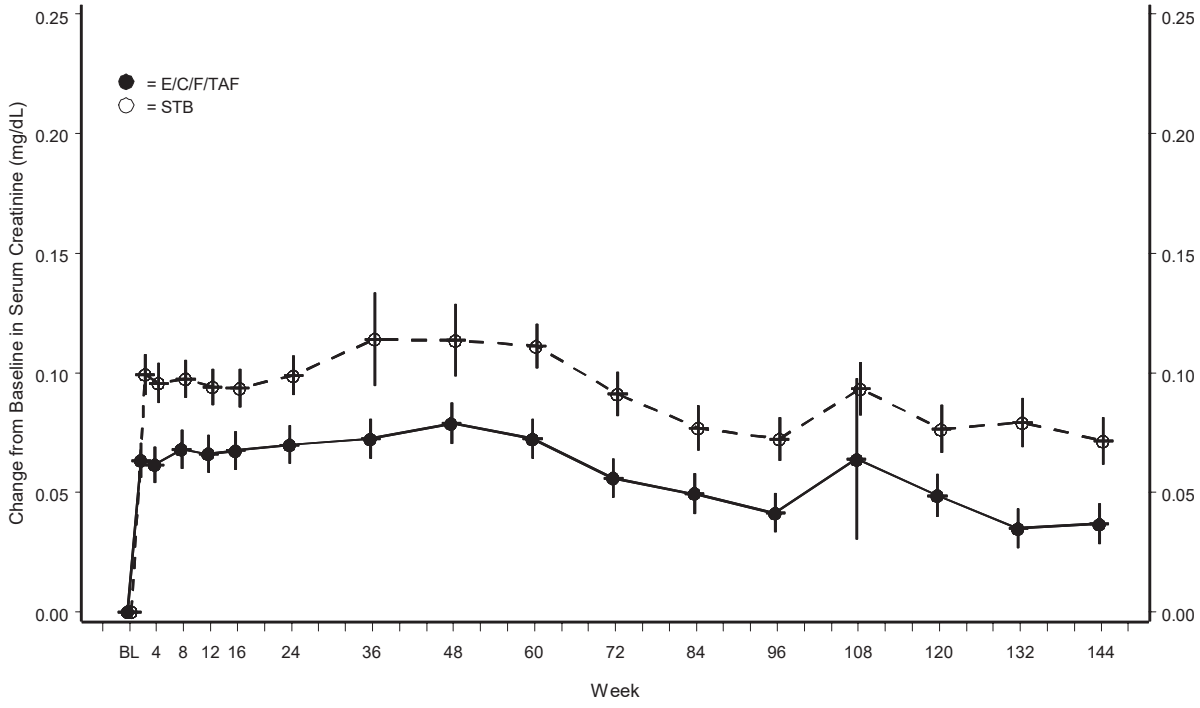
Mean (SD) changes from baseline were as follows:

- Week 2: GEN 0.06 (0.105) mg/dL; STB 0.10 (0.121) mg/dL
- Week 144: GEN 0.04 (0.116) mg/dL; STB 0.07 (0.131) mg/dL

Analysis using LOCF to replace missing values showed similar results to the observed data (GEN Week 144 ISS, Table 26.1).

Graded laboratory abnormalities for serum creatinine were reported as follows: GEN 5.2%, 45 of 862 subjects; STB 7.4%, 64 of 865 subjects (GEN Week 144 ISS, Table 18). Most of these abnormalities were Grade 1. There were no Grade 3 abnormalities in either group. Grade 4 serum creatinine abnormalities were reported as follows: GEN 0.1%, 1 subject; STB 0.2%, 2 subjects.

**Figure 3. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data; Safety Analysis Set)**




| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 866 | 856 | 847 | 843 | 845 | 836 | 830 | 821 | 819 | 805 | 793 | 772 | 767 | 759 | 748 | 741 |
| STB (n=): | 867 | 858 | 852 | 841 | 843 | 834 | 816 | 808 | 793 | 782 | 772 | 758 | 742 | 736 | 727 | 708 |

BL = Baseline.

Data Extracted: s292-0104: CRF,DXA Data: 22JUL2016, Lab Data: 25JUL2016, s292-0111: CRF Data: 28JUL2016, Lab Data: 29JUL2016, DXA Data: 26JUL2016
Source: .../version1/prog/t-lab-creat.sas v9.2 Output file: g-labc-creat-mn.out 09AUG2016:12:08

Source: GEN Week 144 ISS, Figure 5.2

### 2.1.5.2.2.2. Estimated Glomerular Filtration Rate

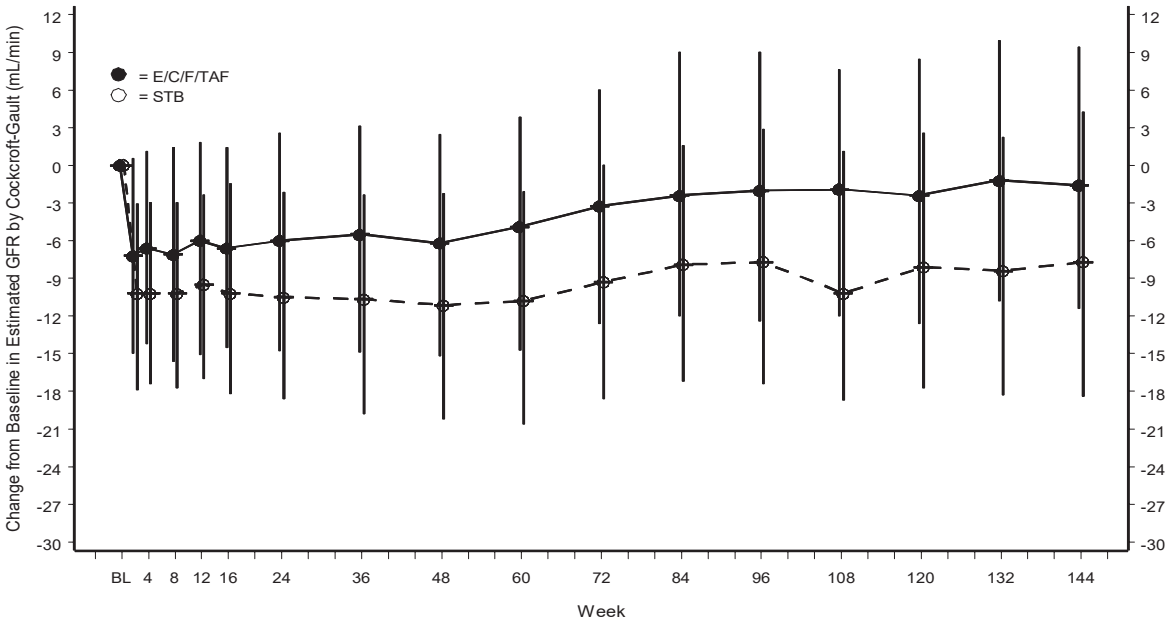
The difference between treatment groups in change from baseline in $eGFR_{CG}$ was statistically significant ($p < 0.001$) at all time points from Weeks 2 through 144. Overall, decreases from baseline in median $eGFR_{CG}$ values were smaller in the GEN group compared with the STB group (Figure 4). Decreases were observed by Week 2 for each treatment group and remained evident through Week 144. Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: GEN 117.0 (99.6, 135.6) mL/min; STB 113.9 (99.0, 133.6) mL/min (GEN Week 144 ISS, Table 27.1).

Median (Q1, Q3) changes from baseline were as follows:

- Week 2: GEN −7.2 (−15.0, 0.5) mL/min; STB −10.2 (−17.9, −3.1) mL/min
- Week 144: GEN −1.6 (−11.4, 9.4) mL/min; STB −7.7 (−18.4, 4.2) mL/min

Observations for changes from baseline in eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI,\ creatinine}$) were consistent with those seen for $eGFR_{CG}$ (GEN Week 144 ISS, Table 27.2).

**Figure 4. GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) Change from Baseline in $eGFR_{CG}$ (mL/min) by Visit (Safety Analysis Set)**




| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 866 854 847 842 845 | 836 | 829 | 821 | 819 | 802 | 792 | 771 | 765 | 759 | 746 | 740 |
| STB (n=): | 867 858 850 841 843 | 833 | 814 | 806 | 793 | 781 | 772 | 756 | 742 | 735 | 727 | 707 |

BL = Baseline.

Data Extracted: s292-0104: CRF,DXA Data: 22JUL2016, Lab Data: 25JUL2016, s292-0111: CRF Data: 28JUL2016, Lab Data: 29JUL2016, DXA Data: 26JUL2016
Source: .../version1/prog/t-lab.sas v9.2 Output file: g-labc-creatclr.out 09AUG2016:12:09

Source: GEN Week 144, Figure 6.1

### 2.1.5.2.2.3. Proteinuria by Urinalysis (Dipstick)

Fewer subjects in the GEN group than the STB group had at least 1 recorded, treatment-emergent graded proteinuria by dipstick urinalysis (GEN 39.6%, 341 of 862 subjects; STB 45.4%, 393 of 865 subjects; p = 0.027; GEN Week 144 ISS, Table 28). Grade 1 proteinuria was reported for most subjects.

### 2.1.5.2.2.4. Proteinuria by Quantitative Assessment

The difference between treatment groups in percentage change from baseline in UPCR was statistically significant from Week 2 through Week 144 ($p < 0.001$ at each time point). There was a decrease from baseline in median UPCR for the GEN group that was observed at Week 2 and persisted through Week 144; in contrast, there was an increase from baseline in UPCR in the STB group. Median (Q1, Q3) percentage changes from baseline at Week 144 were as follows:

GEN −10.5% (−43.9%, 38.0%); STB 25.2% (−23.8%, 95.2%) (Table 10; GEN Week 144 ISS, Table 29.4).

The difference between treatment groups in percentage change from baseline in UACR was statistically significant at both Weeks 48 and 96 ($p < 0.001$ at both time points). A decrease from baseline in median UACR for the GEN group was observed at Week 48 that persisted at Week 96; in contrast, there was an increase from baseline in UACR for the STB group. Median (Q1, Q3) percentage changes from baseline at Week 96 were as follows: GEN −5.2% (−35.6%, 29.7%); STB 5.2% (−32.6%, 59.1%). Only 46 subjects in the GEN group and 59 subjects in the STB group had UACR assessments after Week 96 (GEN Week 144 ISS, Table 29.5).

Urine creatinine was similar for both treatment groups at each measured time point through Week 144 (GEN Week 144 ISS, Table 29.1).

#### 2.1.5.2.2.5. Urine Retinol Binding Protein to Creatinine Ratio and Urine Beta-2-Microglobulin to Creatinine Ratio

The difference between treatment groups in percentage change from baseline in urine RBP to creatinine ratio was statistically significant from Week 2 through Week 144 ($p < 0.001$ at each time point). There was an initial decrease from baseline in urine RBP to creatinine ratio followed by an increase from Week 12 to Week 144 for the GEN group, and a progressive increase from baseline to Week 144 for the STB group. Median (Q1, Q3) percentage changes from baseline at Week 144 were as follows: GEN 34.8% (−4.6%, 83.3%); STB 111.0% (38.4%, 264.9%) (Table 10).

The difference between treatment groups in percentage change from baseline in urine beta-2-microglobulin to creatinine ratio was statistically significant from Week 2 through Week 144 ($p < 0.001$ at each time point). The median percentage change from baseline in urine beta-2-microglobulin to creatinine ratio decreased for the GEN group and increased for the STB group at Week 2 and persisted through Week 144. Median (Q1, Q3) percentage changes from baseline at Week 144 were as follows: GEN −25.7% (−58.2%, 13.7%); STB 53.8% (−26.0%, 305.1%).

**Table 10. GS-US-292-0104 and GS-US-292-0111: Percentage Change from Baseline of Renal Biomarkers at Week 144 (Safety Analysis Set)**

| Parameter | Median Percentage Change (%) (Q1, Q3) | | p-value[a] |
|---|---|---|---|
| | GEN | STB | |
| UPCR (mg/g) | −10.5% (−43.9%, 38.0%) | 25.2% (−23.8%, 95.2%) | < 0.001 |
| UACR (mg/g)[b] | −5.2% (−35.6%, 29.7%) | 5.2% (−32.6%, 59.1%) | < 0.001 |
| Urine RBP to Creatinine Ratio (µg/g) | 34.8% (−4.6%, 83.3%) | 111.0% (38.4%, 264.9%) | < 0.001 |
| Urine Beta-2-microglobulin to Creatinine Ratio (µg/g) | −25.7% (−58.2%, 13.7%) | 53.8% (−26.0%, 305.1%) | < 0.001 |

a P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
b UACR was assessed up to Week 96 and the results at Week 96 were summarized.
Source: GEN Week 144 ISS, Tables 29.2 to 29.5

2.1.5.2.2.6. Other Renal Biomarkers

Other renal biomarkers included the marker of proximal renal tubular function FEUA, measures of renal phosphate handling TmP/GFR, and $FEPO_4$, each using unadjusted and adjusted serum creatinine values.

There were decreases from baseline in median FEUA using adjusted serum creatinine through Week 144 in the GEN group, compared with an increase in the STB group. Median (Q1, Q3) changes from baseline at Week 144 were as follows: GEN −0.1% (−1.4%, 1.2%); STB 1.0% (−0.5%, 2.5%) (GEN Week 144 ISS, Table 33.2).

There were decreases from baseline in median TmP/GFR using adjusted serum creatinine through Week 144 in both treatment groups; the decreases were generally smaller in the GEN group compared with the STB group. Median (Q1, Q3) changes from baseline at Week 144 were as follows: GEN −0.3 (−0.9, 0.2) mg/dL; STB −0.5 (−1.0, 0.0) mg/dL (GEN Week 144 ISS, Table 31.2).

There were increases from baseline in median $FEPO_4$ using adjusted serum creatinine through Week 144 in both treatment groups; the increases were smaller in the GEN group compared with the STB group. Median (Q1, Q3) changes from baseline at Week 144 were as follows: GEN 2.0% (−1.8%, 6.0%); STB 2.8% (−0.8%, 6.7) (GEN Week 144 ISS, Table 32.2).

Results were generally similar for changes in FEUA, TmP/GFR, and $FEPO_4$ calculated using unadjusted serum creatinine (GEN Week 144 ISS, Tables 33.1, 31.1, and 32.1).

#### 2.1.5.3. Potential Cardiovascular and Cerebrovascular Events

Potential cardiovascular and cerebrovascular events are described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 144, Section 11.2.4.3; GS-US-292-0111 Week 144, Section 11.2.4.3).

Potential cardiovascular or cerebrovascular events were reported for similar percentages of subjects in the 2 treatment groups (GEN 2.8%, 24 of 866 subjects; STB 3.8%, 33 of 867 subjects) (GEN Week 144 ISS, Table 17.1). One subject in the GEN group had cerebral infarction that led to discontinuation of study drugs, which was considered not related to study drugs by the investigator. Serious potential cardiovascular or cerebrovascular events were reported as follows: GEN 5 subjects (0.6%; acute myocardial infarction in 2 subjects; cerebral infarction and myocardial infarction, in 1 subject each; and cerebrovascular accident and transient ischemic attack, both in 1 subject; STB 6 subjects (0.7%; acute myocardial infarction in 2 subjects; acute coronary syndrome, cerebrovascular accident, coronary artery disease, and ischemic cardiomyopathy, in 1 subject each) (GEN Week 144 ISS, Table 17.2 and Listing 1). One of these events in the STB group (acute coronary syndrome) was considered by the investigator to be related to study drug. The events of myocardial infarction, cerebrovascular accident, and cerebral infarction in 1 subject each in the GEN group; and acute myocardial infarction in 1 subject in the STB group were fatal.

## 2.2. Narratives

For all Gilead sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures, are provided in the relevant CSRs.

# 3. CLINICAL LABORATORY EVALUATIONS

## 3.1. Laboratory Abnormalities

All laboratory abnormalities discussed in the following sections were treatment-emergent and are referred to as laboratory abnormalities.

Detailed clinical laboratory evaluation results for Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (GS-US-292-0104 Week 144, Section 11.6.3; GS-US-292-0111 Week 144, Section 11.6.3).

Most subjects had at least 1 laboratory abnormality reported during the study (GEN 98.0%, 845 of 862 subjects; STB 96.5%, 835 of 865 subjects; GEN Week 144 ISS, Table 18). The majority of abnormalities were Grade 1 or 2 in severity.

Grade 3 or 4 laboratory abnormalities were reported for similar percentages of subjects in the 2 treatment groups (GEN 32.9%, 284 subjects; STB 30.8%, 266 subjects) (Table 11). The incidence of Grade 3 or 4 laboratory abnormalities was similar in the 2 treatment groups, except for fasting low-density lipoprotein (LDL; see Section 3.2).

The most common Grade 3 or 4 laboratory abnormality was creatine kinase (GEN 11.5%, 99 subjects; STB 10.1%, 87 subjects). Creatine kinase abnormalities occurred at a variety of time points, and were not consistently present for individual subjects. Clinical rhabdomyolysis was reported as an SAE for 3 subjects; 2 subjects in the GEN group and 1 subject in the STB group, all were considered unrelated to study drugs and had alternative explanations (methamphetamine abuse, rigorous exercise, or vaccination; GEN Week 144 ISS, Table 14 and Listing 1). Subjects with serum amylase > 1.5 × upper limit of normal were assessed for lipase abnormalities; among those subjects tested, the incidence of Grade 3 or 4 lipase abnormalities was as follows: GEN 4.7%, 6 subjects; STB 8.4%, 13 subjects. Clinical cases of pancreatitis, however, were low in both groups.

**Table 11. GS-US-292-0104 and GS-US-292-0111: Grade 3 and 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)**

| | GEN (N = 866) | STB (N = 867) |
|---|---|---|
| Maximum Postbaseline Toxicity Grade[a,b] | 862 | 865 |
| Grade 3 or 4 | 284 (32.9%) | 266 (30.8%) |
| Hematology | | |
| Neutrophils | 862 | 865 |
| Grade 3 or 4 | 16 (1.9%) | 26 (3.0%) |
| Chemistry | | |
| ALT | 862 | 865 |
| Grade 3 or 4 | 23 (2.7%) | 25 (2.9%) |
| Amylase | 862 | 865 |
| Grade 3 or 4 | 22 (2.6%) | 43 (5.0%) |
| AST | 862 | 865 |
| Grade 3 or 4 | 29 (3.4%) | 32 (3.7%) |
| Creatine Kinase | 862 | 865 |
| Grade 3 or 4 | 99 (11.5%) | 87 (10.1%) |
| GGT | 862 | 865 |
| Grade 3 or 4 | 10 (1.2%) | 25 (2.9%) |
| Lipase[c] | 127 | 154 |
| Grade 3 or 4 | 6 (4.7%) | 13 (8.4%) |
| Serum Glucose (Fasting, Hyperglycemia) | 860 | 865 |
| Grade 3 or 4 | 9 (1.0%) | 13 (1.5%) |
| Serum Glucose (Nonfasting, Hyperglycemia)[d] | 858 | 857 |
| Grade 3 or 4 | 11 (1.3%) | 11 (1.3%) |
| Total Cholesterol (Fasting, Hypercholesterolemia) | 839 | 835 |
| Grade 3 or 4 | 34 (4.1%) | 23 (2.8%) |
| Triglycerides (Fasting) | 839 | 835 |
| Grade 3 or 4 | 14 (1.7%) | 9 (1.1%) |
| LDL (Fasting) | 839 | 834 |
| Grade 3 or 4 | 92 (11.0%) | 40 (4.8%) |

| | GEN (N = 866) | STB (N = 867) |
|---|---|---|
| Urinalysis[e] | | |
| Urine Glucose (Glycosuria) | 862 | 865 |
| Grade 3 | 15 (1.7%) | 19 (2.2%) |
| Urine RBC (Hematuria, Quantitative) | 862 | 865 |
| Grade 3 | 25 (2.9%) | 26 (3.0%) |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDL = low-density lipoprotein; RBC = red blood cell

a Subjects were counted once at the maximum postbaseline severity for each laboratory test.
b Denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 laboratory value for the test.
c Lipase test was performed only for subjects with serum amylase > 1.5 x upper limit of normal
d For nonfasting glucose, the maximum postbaseline toxicity grade instead of treatment-emergent abnormality was summarized, because a nonfasting glucose test was not done at baseline
e For urinalysis, the highest toxicity grade is Grade 3.

Programming Details: .../version1/prog/t-labtox.sas v9.2 Output file: t-labtox34.out 09AUG2016:12:15
Source: GEN Week 144 ISS, Table 19

## 3.2. Fasting Lipid Parameters

Detailed results of metabolic laboratory parameter evaluations for Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (GS-US-292-0104 Week 144, Section 11.6.5; GS-US-292-0111 Week 144, Section 11.6.5).

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (Table 12). The median increase from baseline for each of these parameters was greater in the GEN group than the STB group ($p < 0.001$). The median (Q1, Q3) change from baseline at Week 144 in the total cholesterol to HDL cholesterol ratio was 0.2 (−0.3, 0.7) in the GEN group and 0.1 (−0.4, 0.6) in the STB group ($p = 0.006$ for the difference between groups).

Consistent with these results, higher percentages of subjects in the GEN group than the STB group had categorical changes in the following National Cholesterol Education Program Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) lipid classifications from baseline at Week 144: fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL): GEN 32.5%, 192 of 591 subjects; STB 20.7%, 118 of 569 subjects; fasting direct LDL cholesterol (< 130 mg/dL to ≥ 130 mg/dL): GEN 30.4%, 168 of 552 subjects; STB 20.6%, 110 of 534 subjects; and triglycerides (< 200 mg/dL to ≥ 200 mg/dL): GEN 14.2%, 92 of 649 subjects; STB 9.4%, 58 of 614 subjects (GEN Week 144 ISS, Tables 34.1.2, 34.2.2, and 34.4.2, respectively). A smaller percentage of subjects in the GEN group than the STB group had a categorical change from baseline in fasting HDL cholesterol (≥ 40 mg/dL to < 40 mg/dL) at Week 144: GEN 5.4%, 26 of 480 subjects; STB 9.8%, 45 of 457 subjects (GEN Week 144 ISS, Table 34.3.2). These small lipid categorical changes were consistent with data from other studies of abacavir, stavudine, and other non TDF-based N(t)RTIs in ART-naive patients {Anastos et al 2007}.

The majority of lipid abnormalities were Grade 1 or 2. Graded fasting hypercholesterolemia was more common in the GEN group than the STB group (GEN 60.5%, 508 subjects; STB 40.1%, 335 subjects; GEN Week 144 ISS, Table 18). More subjects in the GEN group than the STB group had graded abnormalities in fasting LDL cholesterol (GEN 56.3%, 472 subjects; STB 38.5%, 321 subjects). Graded abnormalities in fasting triglycerides were infrequent, and reported for similar percentages of subjects in each treatment group (GEN 4.8%, 40 subjects; STB 3.4%, 28 subjects). Similar percentages of subjects in each treatment group had graded fasting hyperglycemia (GEN 26.3%, 226 subjects; STB 23.8%, 206 subjects).

Adverse events related to lipid laboratory test abnormalities are summarized in GEN Week 144 ISS, Table 7. No lipid laboratory test abnormality AE was serious. One subject in the GEN group who had a Grade 4 laboratory abnormality of elevated triglycerides also had a Grade 3 AE of blood triglycerides increased that resulted in discontinuation of study drugs (and was considered related to study drugs by the investigator; GEN Week 144 ISS, Tables 14 and 16, respectively).

Similar percentages of subjects in each treatment group were taking lipid-modifying medications at study entry (GEN 2.5%, 22 subjects; STB 3.1%, 27 subjects) or initiated lipid-modifying medications during the study (GEN 5.5%, 48 subjects; STB 5.8%, 50 subjects) (GEN Week 144 ISS, Tables 34.6.1 and 34.6.2, respectively).

**Table 12. GS-US-292-0104 and GS-US-292-0111: Summary of Fasting Metabolic Assessments Change from Baseline at Week 144 (Safety Analysis Set)**

| Metabolic Assessment[a] | GEN (N = 866) | STB (N = 867) | p-value[b] |
|---|---|---|---|
| Fasting Total Cholesterol (mg/dL) | | | |
| Baseline | | | |
| N | 841 | 848 | 0.14 |
| Mean (SD) | 164 (36.2) | 166 (37.1) | |
| Median | 160 | 163 | |
| Q1, Q3 | 138, 186 | 140, 189 | |
| Change at Week 144 | | | |
| N | 710 | 686 | < 0.001 |
| Mean (SD) | 31 (31.9) | 13 (31.5) | |
| Median | 31 | 13 | |
| Q1, Q3 | 13, 49 | −5, 30 | |

| Metabolic Assessment[a] | GEN (N = 866) | STB (N = 867) | p-value[b] |
|---|---|---|---|
| Fasting HDL (mg/dL) | | | |
| Baseline | | | |
| N | 841 | 848 | 0.47 |
| Mean (SD) | 46 (13.1) | 45 (12.6) | |
| Median | 44 | 44 | |
| Q1, Q3 | 37, 53 | 37, 52 | |
| Change at Week 144 | | | |
| N | 709 | 686 | < 0.001 |
| Mean (SD) | 6 (11.0) | 3 (11.0) | |
| Median | 6 | 2 | |
| Q1, Q3 | 0, 13 | −3, 9 | |
| Fasting Direct LDL (mg/dL) | | | |
| Baseline | | | |
| N | 837 | 849 | 0.091 |
| Mean (SD) | 105 (31.2) | 108 (33.5) | |
| Median | 101 | 104 | |
| Q1, Q3 | 81, 125 | 85, 126 | |
| Change at Week 144 | | | |
| N | 705 | 687 | < 0.001 |
| Mean (SD) | 19 (28.2) | 7 (27.1) | |
| Median | 19 | 6 | |
| Q1, Q3 | 2, 36 | −8, 21 | |
| Fasting Total Cholesterol to HDL Ratio | | | |
| Baseline | | | |
| N | 841 | 848 | 0.069 |
| Mean (SD) | 3.8 (1.10) | 3.9 (1.22) | |
| Median | 3.6 | 3.6 | |
| Q1, Q3 | 3.0, 4.3 | 3.0, 4.5 | |
| Change at Week 144 | | | |
| N | 709 | 686 | 0.006 |
| Mean (SD) | 0.2 (0.99) | 0.1 (1.00) | |
| Median | 0.2 | 0.1 | |
| Q1, Q3 | −0.3, 0.7 | −0.4, 0.6 | |

| Metabolic Assessment[a] | GEN (N = 866) | STB (N = 867) | p-value[b] |
|---|---|---|---|
| Fasting Triglycerides (mg/dL) | | | |
| Baseline | | | |
| N | 841 | 848 | 0.14 |
| Mean (SD) | 116 (82.4) | 120 (81.7) | |
| Median | 95 | 100 | |
| Q1, Q3 | 70, 137 | 73, 140 | |
| Change at Week 144 | | | |
| N | 710 | 686 | < 0.001 |
| Mean (SD) | 30 (90.6) | 16 (79.2) | |
| Median | 20 | 12 | |
| Q1, Q3 | −8, 58 | −16, 46 | |

a Only laboratory measurements under fasting status were summarized.
b P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GEN Week 144 ISS, Tables 34.1.1, 34.2.1, 34.3.1, 34.4.1, and 34.5

# 4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Detailed information on vital signs, physical findings, and other observations related to safety for Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (GS-US-292-0104 Week 144, Section 11.7; GS-US-292-0111 Week 144, Section 11.7).

# 5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

## 5.1. Intrinsic Factors

### 5.1.1. Sex

The percentages of subjects experiencing any AE were comparable in males and females for both treatment groups, as follows: GEN: male 94.5%, 693 of 733 subjects; female 93.2%, 124 of 133 subjects; STB: male 96.5%, 714 of 740 subjects; female 93.7%, 119 of 127 subjects (GEN Week 144 ISS, Table 8.2). Individual AEs were generally similar in males and females in both treatment groups.

### 5.1.2. Age

The percentages of subjects experiencing any AE were comparable in subjects < 50 and ≥ 50 years of age for both treatment groups, as follows: GEN: < 50 years 94.1%, 731 of 777 subjects; ≥ 50 years 96.6%, 86 of 89 subjects; STB < 50 years 96.0%, 723 of 753 subjects; ≥ 50 years 96.5%, 110 of 114 subjects (GEN Week 144 ISS, Table 8.1).

### 5.1.3. Race

The percentages of subjects experiencing any AE were comparable in black and nonblack subjects, as follows: GEN: black 94.6%, 211 of 223 subjects; nonblack 94.2%, 606 of 643 subjects; STB: black 95.8%, 204 of 213 subjects; nonblack 96.2%, 629 of 654 subjects (GEN Week 144 ISS, Table 8.3).

### 5.1.4. HIV-1 RNA Stratum at Baseline

The percentages of subjects experiencing any AE were comparable in subjects with baseline HIV-1 RNA level ≤ 100,000 copies/mL and > 100,000 copies/mL for both treatment groups, as follows: GEN: ≤ 100,000 copies/mL 94.2%, 631 of 670 subjects; > 100,000 copies/mL 94.9%, 186 of 196 subjects; STB ≤ 100,000 copies/mL 95.5%, 642 of 672 subjects; > 100,000 copies/mL 97.9%, 191 of 195 subjects (GEN Week 144 ISS, Table 8.4).

### 5.1.5. CD4 Cell Count at Baseline

The percentages of subjects experiencing any AE were comparable in subjects with baseline CD4 cell count < 200 cells/µL and ≥ 200 cells/µL for both treatment groups, as follows: GEN CD4 cell count < 200 cells/µL 92.9%, 104 of 112 subjects; ≥ 200 cells/µL 94.6%, 712 of 753 subjects; STB CD4 cell count < 200 cells/µL 96.6%, 113 of 117 subjects; ≥ 200 cells/µL 96.0%, 720 of 750 subjects (GEN Week 144 ISS, Table 8.5).

## 5.2. Extrinsic Factors

### 5.2.1. Region

The percentages of subjects experiencing any AE were comparable in subjects from the US and ex-US regions for both treatment groups, as follows: GEN: US 93.8%, 499 of 532 subjects; ex-US 95.2%, 318 of 334 subjects; STB: US 96.6%, 514 of 532 subjects; ex-US 95.2%, 319 of 335 subjects (GEN Week 144 ISS, Table 8.6).

## 5.3. Drug Interactions

No new information is submitted.

## 5.4. Use in Pregnancy and Lactation

Pregnancies were reported for 11 subjects (GEN 2 subjects; STB 9 subjects). All but 1 subject discontinued study drugs. One of the subjects in the GEN group underwent an induced abortion due to omphalocele, suspected by the investigator to have been related to exposure to GEN. The fetus was subsequently reported to have trisomy 18, which is commonly associated with omphalocele. The pregnancy of the other subject in the GEN group was continuing and an outcome is not available; this subject was later considered lost to follow-up.

Thirteen confirmed pregnancies were reported for the 9 subjects in STB group through Week 144. The results of the pregnancies in the STB group are provided in Table 13.

**Table 13. GS-US-292-0104 and GS-US-292-0111: Pregnancy Results in the STB Group**

| Results of Pregnancies | Number of Neonates/Pregnancies/Subject |
|---|---|
| Delivery of a healthy baby without complication | 3 |
| Unknown status of the current pregnancy | 2 |
| Continuing | 2 |
| Miscarriage | 1 |
| Spontaneous abortion | 1 |
| Cryptorchidism | 1 |
| Severe intrauterine growth restriction[a] | 1 |
| Broken leg[b] | 1 |
| Delivery of a healthy baby with complications[c] | 1 |

a Reported as not a Metropolitan Atlanta Congenital Defects Program defect.
b Broken leg was reported for the neonate, with possible cause reported as delivery.
c The subject had a uterine rupture, which the investigator noted to be normal spontaneous rupture of membrane (water breaking), and a decreased platelet count (the subject received a transfusion while in the hospital).
Source: GS-US-292-0104 Week 144, Section 11.8 and GS-US-292-0111 Week 144, Section 11.8

## 5.5. Overdose

No new safety issues have been identified regarding overdose since the original marketing application.

## 5.6. Drug Abuse

No safety issues concerning the abuse or misuse of GEN tablets are anticipated from the available data.

## 5.7. Withdrawal and Rebound

No new information is presented.

## 5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of EVG, COBI, FTC, or TAF on the ability to drive or operate machinery.

# 6. POSTMARKETING DATA

Postmarketing safety data for GEN and its individual components are carefully evaluated on an ongoing basis for any new safety issues, and labeling changes are submitted to regulatory authorities when new adverse reactions are identified. There have been no newly identified adverse reactions for GEN based on the postmarketing data available to date.

# 7. REFERENCES

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# 8. APPENDIX

| Appendix Number | Appendix Title |
|---|---|
| 8.1 | GEN Fixed Dose Combination Integrated Safety Analyses |

## 8.1. GEN Fixed-Dose Combination Integrated Safety Analyses

The following tables, figures, and listings (TFLs) present pooled data from Studies GS-US-292-0104 and GS-US-292-0111. All the TFLs were based on the safety analysis set except for the subject disposition table, which was based on all screened subjects. These outputs are described in the ISS SAP.

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**SECTION 2.7**
**CLINICAL SUMMARY**

**SECTION 2.7.5—LITERATURE REFERENCES**

# EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (FTC/RPV/TAF FDC)

Gilead Sciences

25 June 2015

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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**SECTION 2.7**
**CLINICAL SUMMARY**

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**SECTION 2.7.5—LITERATURE REFERENCES**

# DESCOVY®
# (EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

Gilead Sciences

01 August 2016

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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**SECTION 2.7**
**CLINICAL SUMMARY**

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**SECTION 2.7.5—LITERATURE REFERENCES**

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)
# SUBMISSION REF. NO. : ODE-16-080
# (STUDY GS-US-366-1160)

Gilead Sciences

27 October 2016

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# 1. LITERATURE REFERENCES

The following references are cited in the Clinical Summary documents (ie, m2.7.1 to m2.7.4). Copies of these references are available upon request if not provided with this submission.

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Revision 1. November 2015.

**SECTION 2.7**
**CLINICAL SUMMARY**

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**SECTION 2.7.5—LITERATURE REFERENCES**

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)
# SUBMISSION REF. NO. : ODE-16-080
# (STUDY GS-US-366-1216)

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27 October 2016

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# 1. LITERATURE REFERENCES

The following references are cited in the Clinical Summary documents (ie, m2.7.1 to m2.7.4). Copies of these references are available upon request if not provided with this submission.

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Revision 1. November 2015.

**SECTION 2.7**
**CLINICAL SUMMARY**

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## SECTION 2.7.5—LITERATURE REFERENCES

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

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Moyle GJ, Stellbrink HJ, Compston J, Orkin C, Arribas JR, Domingo P, et al. 96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study. Antivir Ther 2013;18 (7):905-13.

Qaqish R, Trinh R, Tian M, Fredrick L, Podsadecki T, Norton M, et al. Bone mineral density (BMD) analysis in antiretroviral (ART)-naïve subjects taking Lopinavir/Ritonavir (LPV/R) combined with Raltegravir (RAL) or Tenofovir/Emtricitabine (TDF/FTC) for 96 weeks in the PROGRESS study [Abstract O09]. Presented at:13th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV; 2011 July 14-16; Rome, Italy. Antivir Ther 2011;16 (Suppl. 2):A8.

**SECTION 2.7.6— SYNOPSES OF INDIVIDUAL STUDIES**

# EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFEMANIDE FIXED-DOSE COMBINATION (FTC/RPV/TAF FDC)

Gilead Sciences

21 July 2015

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# 1. LISTING OF CLINICAL STUDIES

## 1.1. FTC/RPV/TAF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Comparative BA/BE | GS-US-366-1159 (synopsis) | Evaluate the bioequivalence of FTC and TAF administered as FTC/RPV/TAF FDC or E/C/F/TAF FDC and evaluate the bioequivalence of RPV administered as RPV or FTC/RPV/TAF FDC | Phase 1, randomized, open-label, single-dose, 3-way, 6-sequence crossover study | Subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA) and received the following treatments:<br>• FTC/RPV/TAF 200/25/25 mg FDC PO (A)<br>• RPV 25 mg FDC PO (B)<br>• E/C/F/TAF 150/150/200/10 mg FDC PO (C) | 3 days (single doses on Days 1, 15, and 29) | Randomized: 96<br>Completed: 94<br>Safety Analysis Set: 96<br>A: 95<br>B: 95<br>C: 96 | Healthy adult subjects | Study completed; m5.3.1.2<br>Final CSR |
| Extrinsic Factor PK | GS-US-366-1651 (synopsis) | Determine the effect of food on the PK of FTC, RPV, and TAF when administered as a FTC/RPV/TAF FDC | Phase 1, randomized, open-label, single-dose, 2-period crossover study | Subjects in each cohort were randomized to 1 of 2 treatment sequences (Cohort 1: AB or BA, Cohort 2: AC or CA) and received FTC/RPV/TAF (200/25/25 mg) PO administered under the following conditions:<br>• Fasted (A)<br>• Light/low-fat food (B)<br>• High-calorie/high-fat food (C) | 2 days (single doses on Days 1 and 11) | Randomized: 60<br>Completed: 60<br>Safety Analysis Set: 60<br>A: 60<br>B: 30<br>C: 30 | Healthy adult subjects | Study completed; m5.3.3.4<br>Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-366-1689 (synopsis) | Evaluate the PK of FTC, RPV, TAF, LDV, SOF, and the SOF metabolites GS-566500 and GS-311007 when coadministered as FTC/RPV/TAF FDC with LDV/SOF FDC | Phase 1, randomized, open-label, multiple-dose, 3-way, 6-sequence crossover study | Subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA) and received the following treatments:<br>• LDV/SOF 90/400 mg FDC PO (A)<br>• FTC/RPV/TAF 200/25/25 mg FDC PO (B)<br>• LDV/SOF 90/400 mg + FTC/RPV/TAF 200/25/25 mg FDC PO (C) | 33 days total (Regimens A, B, and C administered 11 days each) | Randomized: 42<br>Completed: 41<br>Safety Analysis Set: 42<br>A: 42<br>B: 42<br>C: 42 | Healthy adult subjects | Study completed;<br>m 5.3.3.4<br>Final CSR |

## 1.2. F/TAF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-311-0101 (synopsis) | Cohort 1: Evaluate the PK of TAF, TFV, and FTC following once-daily coadministration of F/TAF FDC and EFV relative to the administration of F/TAF FDC alone<br>Cohorts 2 and 3: Evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF FDC and DRV+COBI relative to the administration of these agents alone<br>Cohort 4: Evaluate the PK of TAF, TFV, and COBI following once-daily coadministration of TAF+COBI relative to the administration of TAF alone | Phase 1, nonrandomized, open-label, crossover, multicohort, multiple-dose study | Cohort 1:<br>• F/TAF (200/40 mg) QD PO (Days 1-12, fasted) (A)<br>• F/TAF (200/40 mg) + EFV 600 mg QD PO (Days 13-26, fasted) (B)<br>Cohort 2:<br>• F/TAF (200/25 mg) QD PO (Days 1-12, fed) (C)<br>• F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 13-22, fed) (D)<br>Cohort 3:<br>• DRV 2 × 400 mg + COBI 150 mg QD PO (Days 1-10, fed) (E)<br>• F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) | Cohort 1: 26 days<br>Cohorts 2-4: 22 days | Enrolled:50<br>Completed: 48<br>Safety Analysis Set:<br>A: 12<br>B: 12<br>C: 12<br>D: 25[a]<br>E: 14<br>F: n/a<br>G: 12<br>H: 12<br>[a] Includes 11 subjects who received Treatment D and 14 subjects who received Treatment F | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| | | | | Cohort 4:<br>• TAF 8 mg QD PO (Days 1-12, fed) (G)<br>• TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H) | | | | |

## 1.3. E/C/F/TAF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PK and Tolerability Healthy Subject PK and Tolerability | GS-US-292-0101 (synopsis) | Evaluate the relative bioavailability of EVG, COBI, FTC, and TFV when administered as 1 of 2 formulations of E/C/F/TAF FDC vs STB STR and TAF alone | Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort study | Within each cohort, subjects were randomized to 1 of 4 treatment sequences and received the following treatment:<br>Cohort 1:<br>• Formulation 1 E/C/F/TAF (150/150/200/25 mg) QD PO (A)<br>• Formulation 1 E/C/F/TAF (150/150/200/40 mg) QD PO (B)<br>• STB STR (150/150/200/300 mg) QD PO (C)<br>• TAF 25 mg QD PO (D)<br>Cohort 2:<br>• Formulation 2 E/C/F/TAF (150/150/200/25 mg) QD PO (E)<br>• Formulation 2 E/C/F/TAF (150/150/200/40 mg) QD PO (F)<br>• STB STR (150/150/200/300 mg) QD PO (C)<br>• TAF 25 mg QD PO (D) | 54 days (4 12-day treatment sequences with a 2-day washout period between each sequence) | Randomized: 40<br>Completed: 36<br>Safety Analysis Set:<br>Cohort 1: 20<br>Cohort 2: 20 | Healthy adult subjects | Study completed; m5.3.3.1, Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-292-0102 (synopsis) | Evaluate the efficacy of a regimen containing E/C/F/TAF FDC versus STB STR | Phase 2, randomized, double-blind and open-label, multicenter, active-controlled study | Randomized Phase:<br>• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A)<br>• STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B)<br>Open-Label Extension Phase:<br>• E/C/F/TAF (150/150/200/10 mg) QD PO (C) | Randomized Phase: 48 weeks until unblinding<br>Open-Label Extension Phase: Until E/C/F/TAF is commercially available or development is terminated | Randomized: 171<br>Completed: 158<br>Safety Analysis Set:<br>A: 112<br>B: 58<br>Entered Open-Label Extension:<br>A: 105<br>B: 53<br>299-0102: 108<br>Continuing study drug at Week 96:<br>A: 104<br>B: 53<br>299-0102: 107 | Randomized Phase: HIV infected, ART-naive adult subjects<br>Open-Label Extension Phase: Additional HIV infected adult subjects had received a DRV+COBI containing regimen in Study GS-US-299-0102 and were ART-naive at the time of entry into that study. | Study ongoing; m5.3.5.1, Week 96 Interim CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Comparative BA/BE | GS-US-292-0103 (synopsis) | Evaluate the PK and relative bioavailability of EVG, COBI, FTC, TAF, and TFV administered as E/C/F/TAF FDC relative to the administration of the individual components | Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort, 2-period, crossover study | Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments:<br>Cohort 1:<br>• E/C/F/TAF (150/150/200/10 mg) QD PO (A)<br>• EVG 150 mg + COBI 150 mg QD PO (B)<br>Cohort 2:<br>• E/C/F/TAF (150/150/200/10 mg) QD PO (A)<br>• FTC 200 mg + TAF 25 mg QD PO (C) | 24 days (12 days for each treatment period within a sequence) | Randomized: 34<br>Completed: 33<br>Safety Analysis Set:<br>Cohort 1: 14<br>Cohort 2: 20 | Healthy adult subjects | Study completed; m5.3.1.2, Final CSR |
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-292-0104 (synopsis) | Evaluate the efficacy of E/C/F/TAF FDC versus STB STR | Phase 3, randomized, double-blind, active-controlled, multicenter study | • E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A)<br>• STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B) | 96 weeks<br>Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated | Randomized: 872<br>Safety Analysis Set:<br>A: 435<br>B: 432<br>Continuing study drug at Week 48:<br>A: 413<br>B: 400 | HIV infected, ART-naive adult subjects | Study ongoing; m5.3.5.1, Week 48 Interim CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | GS-US-292-0106 (synopsis) | Part A: Evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC<br>Part B: Evaluate the safety and tolerability of the E/C/F/TAF FDC | Phase 2/3, open-label, multicenter, 2-part, single-group study | • E/C/F/TAF (150/150/200/10 mg) QD PO | 48 weeks<br>Extension Phase: Subjects have option to continue study drug until subject turns 18 and E/C/F/TAF is commercially available for adults in country of enrollment, E/C/F/TAF becomes commercially available for adolescents in country of enrollment, or E/C/F/TAF development is terminated in country of enrollment | Enrolled: 48<br>Part A: 24<br>Part B: 24<br>Safety Analysis Set: 48<br>Continuing study drug at Week 24:<br>Main study: 47<br>Extension: 1 | HIV infected, ART-naive adolescents (12 to < 18 years of age) | Study ongoing; m5.3.5.2, Week 24 Interim CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PK and Tolerability | GS-US-292-0108 (synopsis) | Investigate the PK of EVG, COBI, FTC, TAF, and TFV when administered as E/C/F/TAF FDC in healthy Japanese and Caucasian subjects | Phase 1, open-label, sequential single- and multiple-dose study | • E/C/F/TAF (150/150/200/10 mg) QD PO | 13 days (1 single dose on Day 1, followed by a washout and then once-daily doses of study treatment on Days 8 to 19 | Enrolled: 20<br>Completed: 17<br>Safety Analysis Set:<br>Single-dose phase: 20 (10 Japanese; 10 Caucasian)<br>Multiple-dose phase: 18 (10 Japanese; 8 Caucasian) | Healthy adult Japanese (first generation Japanese descent) or Caucasian (not of Japanese or Asian descent) subjects | Study completed; m5.3.3.1, Final CSR |
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-292-0109 (synopsis) | Evaluate the noninferiority of switching to a TAF-containing FDC relative to maintaining TDF-containing regimens in virologically suppressed, HIV infected subjects | Phase 3, randomized, open-label, active-controlled, multicenter study | • Switch to E/C/F/TAF (150/150/200/10 mg) QD PO from a predefined FTC/TDF regimen (A)<br>• Stay on pre-existing FTC/TDF+3rd Agent regimen (B):<br>STB STR (150/150/200/300 mg) QD PO;<br>ATR STR (600/200/300 mg) QD PO;<br>ATV 300 mg + COBI 150 mg + FTC/TDF (200/300 mg) QD PO; or<br>ATV 300 mg + RTV 100 mg + FTC/TDF (200/300 mg) QD PO | 96 weeks<br>Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated | Randomized: 1443<br>Safety Analysis Set:<br>A: 959<br>B: 477<br>Continuing study drug at Week 48:<br>A: 939<br>B: 447 | HIV infected adult subjects from a predefined set of Gilead clinical studies receiving ARV regimens for at least 6 consecutive months, and who had maintained plasma HIV-1 RNA levels at undetectable levels for ≥ 6 consecutive months prior to screening | Study ongoing; m5.3.5.1, Week 48 Interim CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-292-0110 (synopsis) | Evaluate the effect of food (high-calorie/high-fat meal or light/low-fat meal) on the PK of TAF when administered as E/C/F/TAF FDC | Phase 1, randomized, open-label, single-center, 3-period, 6-sequence, crossover, food-effect study | Subjects were randomized to 1 of 6 treatment sequences and received E/C/F/TAF (150/150/200/10 mg) QD PO administered under the following meal conditions:<br>• Fasted (A)<br>• Light/low-fat meal (B)<br>• High-calorie/high-fat meal (C) | 15 days (study drug was administered on Days 1, 8, and 15) | Randomized: 43<br>Completed: 42<br>Safety Analysis Set: 43 | Healthy adult subjects | Study completed; m5.3.3.4, Final CSR |
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-292-0111 (synopsis) | Evaluate the efficacy of E/C/F/TAF FDC versus STB STR | Phase 3, randomized, double-blind, active-controlled, multicenter study | • E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A)<br>• STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B) | 96 weeks<br>Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated | Randomized: 872<br>Safety Analysis Set:<br>A: 431<br>B: 435<br>Continuing study drug at Week 48:<br>A: 408<br>B: 396 | HIV infected, ART-naive adult subjects | Study ongoing; m5.3.5.1, Week 48 Interim CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | GS-US-292-0112 (synopsis) | Evaluate the effect of the E/C/F/TAF FDC on renal parameters | Phase 3, open-label, multicenter, multi-cohort study | • E/C/F/TAF (150/150/200/10 mg) QD PO | 96 weeks<br>Extension Phase: Subjects have option to continue study drug until E/C/F/TAF is commercially available or development is terminated | Enrolled: 252<br>Safety Analysis Set:<br>Cohort 1: 242<br>Cohort 2: 6<br>Continuing study drug at Week 24<br>Cohort 1: 226<br>Cohort 2: 6 | HIV-infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min<br>Cohort 1: ART-experienced<br>Cohort 2: ART-naive | Study ongoing;<br>m5.3.5.2, Week 24 Interim CSR |

## 1.4. TAF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Patient PD and PK/PD | GS-US-120-0104 (synopsis) | Evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg compared to placebo-to-match TAF or TDF 300 mg | Phase 1, randomized, partially-blinded, active- and placebo-controlled study | • TAF 8 mg QD PO (A)<br>• TAF 25 mg QD PO (B)<br>• TAF 40 mg QD PO (C)<br>• TDF 300 mg QD PO (D)<br>• Placebo-to-match TAF QD PO (E) | 10 days | Randomized: 40<br>Completed: 37<br>Safety Analysis Set:<br>A: 9<br>B: 8<br>C: 8<br>D: 6<br>E: 7 | HIV-infected adult subjects, who had not received ART within 90 days of screening | Study completed;<br>m5.3.4.2 Final CSR |
| Healthy Subjects PK and PK/PD | GS-US-120-0107 (synopsis) | Evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF | Phase 1, randomized, partially-blinded, placebo- and positive-controlled, 4-period, single-dose crossover study | Subjects were randomized to 1 of 8 treatment sequences and received the following treatments:<br>• TAF 25 mg + 4 × placebo-to-match TAF QD PO (A)<br>• TAF 125 mg (5 × 25 mg) QD PO (B)<br>• Placebo-to-match TAF (C)<br>• Moxifloxacin 400 mg PO, administered open-label (D) | 37 days (4 single-dose treatment days separated by 11 days of washout between doses) | Randomized: 59<br>Completed: 58<br>Safety Analysis Set:<br>A: 58<br>B: 58<br>C: 59<br>D: 58 | Healthy adult subjects | Study completed;<br>m5.3.4.1 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Intrinsic Factor PK | GS-US-120-0108 (synopsis) | Evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with and without severe renal impairment | Phase 1, open-label, parallel-design, single-dose, PK study | • TAF 25 mg PO | Single dose | Enrolled: 27<br>Completed: 27<br>Safety Analysis Set:<br>Subjects with severe renal impairment: 14<br>Age and sex matched controls: 13 | Adult subjects with severe renal impairment ($eGFR_{CG}$ of 15 to ≤ 29 mL/min) or healthy matched control subjects ($eGFR_{CG}$ of ≥ 90 mL/min) | Study completed;<br>m5.3.3.3 Final CSR |
| Healthy Subject PK and Tolerability | GS-US-120-0109 (synopsis) | Determine the mass balance of TAF following administration of a single, oral dose of radiolabeled [$^{14}$C]TAF | Phase 1, open-label, mass-balance study | • TAF 25 mg (mixture of unlabeled TAF and [$^{14}$C]TAF) PO | Single dose | Enrolled: 8<br>Completed: 8<br>Safety Analysis Set: 8 | Healthy adult male subjects | Study completed;<br>m5.3.3.1 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Intrinsic Factor PK | GS-US-120-0114 (synopsis) | Evaluate the PK of TAF in subjects with normal and impaired hepatic function | Phase 1, open-label, 2-cohort, parallel-group, single-dose, multicenter study | • TAF 25 mg PO | Single dose | Enrolled: 40<br>Completed: 40<br>Safety Analysis Set:<br>Cohort 1:<br>Subjects with mild hepatic impairment: 10<br>Matched controls: 10<br>Cohort 2:<br>Subjects with moderate hepatic impairment: 10<br>Matched controls: 10 | Cohort 1: Adult subjects with mild hepatic impairment (CPT Class A) and healthy matched control subjects<br>Cohort 2: Adult subjects with moderate hepatic impairment (CPT Class B) and healthy matched control subjects | Study completed;<br>m5.3.3.3 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Patient PD and PK/PD | GS - 120-1101 (synopsis) | Investigate the safety of TAF over 14 days, and evaluate the antiviral potency of escalating doses of TAF compared with TDF in ARTnaive HIV infected subjects | Phase 1/2, randomized, double-blind, active controlled, dose-escalation study | Within each cohort, subjects were randomized to 1 of the following treatments:<br>Cohort 1:<br>• TAF 50 mg (2 × 25-mg tablets) + placebo-to-match TDF QD PO (A)<br>• Placebo-to-match TAF + TDF 300-mg tablet QD PO (B)<br>Cohort 2:<br>• TAF 150 mg (6 × 25-mg tablets) + placebo-to-match TDF QD PO (C)<br>• Placebo-to-match TAF + TDF 300-mg tablet QD PO (D) | 14 days | Randomized: 30<br>Completed: 30<br>Safety Analysis Set:<br>A: 10<br>B + D: 10<br>C: 10 | HIV infected, ART-naive adult subjects | Study completed; m5.3.4.2, Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-120-1538 (synopsis) | Evaluate the PK and drug interaction potential between TAF and MDZ (Oral and IV) | Phase 1, open-label, multiple-dose, single-center study | Subjects received the following treatments in a fixed sequence under fed conditions in the morning:<br>• Day 1: $MDZ_{oral}$ 2.5 mg syrup (A)<br>• Day 3: $MDZ_{IV}$ 1 mg solution (B)<br>• Days 4-15 and 17: TAF 25 mg PO (C)<br>• Day 16: TAF 25 mg PO + $MDZ_{oral}$ 2.5 mg syrup coadministered (D)<br>• Day 18: TAF 25 mg PO + $MDZ_{IV}$ 1 mg solution administered within 5 min of each other (E) | 18 days (Day 1, washout on Day 2, and doses on Days 3-18) | Enrolled: 18<br>Completed: 18<br>Safety Analysis Set:<br>A: 18<br>B: 18<br>C: 18<br>D: 18<br>E: 18 | Healthy adult subjects | Study completed; m5.3.3.4 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-120-1554 (synopsis) | Evaluate the PK and drug interaction potential between TAF and RPV | Phase 1, open-label, randomized, fixed-sequence, 2-cohort, 2-period, multiple-dose study | Within each cohort, subjects were randomized to 1 of 2 treatment cohorts and received the following treatments under fed conditions:<br>Cohort 1:<br>• TAF 25 mg QD PO (Days 1-14) (A)<br>• TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C)<br>Cohort 2:<br>• RPV 25 mg QD PO (Days 1-14) (B)<br>• TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C) | 28 days | Randomized: 34<br>Completed: 32<br>Safety Analysis Set:<br>Cohort 1: 17<br>Cohort 2: 17 | Healthy adult subjects | Study completed; m5.3.3.4 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-120-0117 (synopsis) | Evaluate the PK drug interaction potential between RPV and TAF | Phase 1, open-label, single-center, single-dose, crossover study | Enrolled in 1 of the following 2 cohorts to receive 2 treatments under fed conditions:<br>Cohort 1:<br>• TAF 25 mg (A)<br>• TAF 25 mg + RPV 25 mg (B)<br>Cohort 2:<br>• TAF 25 mg + RPV 25 mg (B)<br>• RPV 25 mg (C) | 2 days | Randomized: 36 subjects completed<br>Safety analysis and all PK analysis set:<br>Cohort 1: 18<br>Cohort 2: 18 | Healthy adult subjects | Study completed; m5.3.3.4<br>Final CSR |

## 1.5. FTC

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Patient PK and Initial Tolerability | Burroughs Wellcome 143-001 (synopsis) | Assess the safety, PK, and effect of food on the BA of FTC | Phase 1, randomized, single-blind, single-dose, placebo-controlled, escalating doses (100 to 1200 mg) | • Single escalating oral doses of FTC administered as capsules: 100, 200, 400 (± food), 800, and 1200 mg, PO<br>• Placebo, PO | 6 total doses, each given 1 week apart | Enrolled: 18<br>Active: 12<br>Placebo: 6<br>Completed: 17 | HIV-infected adult subjects | Study completed; m5.3.3.2 Final CSR |
| Patient PK and Initial Tolerability | FTC-101 (synopsis) | Evaluate the safety, tolerance, PK, and antiviral activity of repeat doses of FTC | Phase 1, open-label, dose-ranging study with 14 days of repeated doses of monotherapy | Multiple escalating oral doses of FTC administered as capsules for:<br>25 mg BID (N = 9)<br>100 mg BID (N = 8)<br>200 mg BID (N = 8)<br>100 mg QD (N = 8)<br>200 mg QD (N = 8) | 14 days | Enrolled: 41<br>Completed: 41 | HIV-infected, therapy-naive adult subjects | Study completed; m5.3.3.2 Final CSR |
| Patient PK and Initial Tolerability | FTC-102 (synopsis) | Safety, antiviral activity, dose-defining, comparison with 3TC | Phase 1/2, randomized, open-label, 3TC-controlled, 3 doses of FTC, 10-day repeated doses of monotherapy in adult HIV infected, ART-naive patients | • FTC 25 mg QD PO (N = 20) (A)<br>• FTC 100 mg QD PO (N = 21) (B)<br>• FTC 200 mg QD PO (N = 19) (C)<br>• 3TC 150 mg BID PO (N = 21) (D) | 10 days | As treated: 81<br>Completed: 81<br>Safety Analysis Set: 81 | HIV-infected adult subjects | Study completed m5.3.3.2; Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PK and Tolerability | FTC-106 (synopsis) | Evaluate ADME of [$^{14}$C]FTC, mass balance by urinary and fecal recovery, plasma and PBMCs (FTC-triphosphate) | Phase 1, open-label, single-dose and 8-day repeated doses of FTC (with a single [$^{14}$C]FTC dose) in healthy adult volunteers | • Day 1: 200 mg single dose PO (N = 6)<br>• Days 3−11: 200 mg QD PO for 8 days, single 250 µCi [$^{14}$C]FTC dose PO on the last day (N = 5) | 11 days | Enrolled: 6<br>Completed: 5<br>Safety Analysis Set: 6 | Healthy male subjects | Study completed;<br>m5.3.3.1 Final CSR |
| Intrinsic Factor PK | FTC-107 (synopsis) | Assess the PK profiles in subjects with various degrees of renal insufficiency (for potential dosage adjustment) and effect of hemodialysis | Phase 1, open-label, single dose study of FTC in adult volunteers with varying degrees of renal insufficiency without and with hemodialysis | Single dose of FTC 200 mg administered PO in capsule formulation to:<br>• Group 1 (normal renal function, CLCr > 80 mL/min, N = 6)<br>• Group 2 (mild renal impairment, CLCr = 50−80 mL/min, N = 6)<br>• Group 3 (moderate renal impairment, CLCr = 30−49 mL/min, N = 6)<br>• Group 4 (severe renal impairment, CLCr < 30 mL/min, N = 5)Group 5 (functional anephric, N = 6) | 1 single dose (Groups 1 to 4), 2 single doses separated by a 7-day washout period (Group 5) | Enrolled: 29<br>Completed: 29 | Adult subjects with varying degrees of renal insufficiency with and without hemodialysis | Study completed;<br>m5.3.3.3 Final CSR<br>Dosing Interval Report |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | FTC-108 (synopsis) | Assess potential PK interactions with concomitant antiviral drug (ie, famciclovir) with extensive renal excretion | Phase 1, randomized, open-label, single-dose, 3-way crossover study | 3 single crossover doses (all PO) of:<br>• FTC 200 mg alone<br>• FCV 500 mg alone<br>• FTC 200 mg + FCV 500 mg<br>1-week washout interval between doses | 2 single doses | Enrolled: 12<br>Completed: 12<br>Safety Analysis Set: 12 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR |
| BA | FTC-110 (synopsis) | Evaluate relative and absolute BA of FTC | Phase 1, open-label, randomized, 3-way crossover, single 200-mg doses administered as IV solution, oral solution, or oral capsule | • FTC 1 × 200-mg capsule, PO, fasted (A)<br>• 20 mL of FTC 10 mg/mL solution, PO, fasted (B)<br>• 20 mL of FTC 10 mg/mL solution, IV infused over 1 hour, fasted (C) | 3 single doses | Enrolled: 12<br>Completed: 12<br>Safety Analysis Set: 12 | Healthy adult subjects | Study completed;<br>m5.3.1.1 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | FTC 203 (synopsis) | Obtain long-term safety, PK, and antiviral activity of FTC in pediatric subjects | Phase 2, multicenter, open-label study in ART-naive and ART-experienced male or female pediatric patients.<br>ART-naive patients had no or very limited prior ART exposure. | ART-naive (triple-drug ART regimen):<br>• FTC (6 mg/kg QD; up to 200 mg capsule or 240 mg oral solution QD)<br>• d4T (mg/kg BID dosage based on weight): 1 mg/kg (< 30 kg); 30 mg/kg (30–59 kg); 40 mg/kg (≥ 60 kg)<br>• LPV/r (mg/kg BID dosage based on weight): 12/3 mg/kg (7-< 15 kg); 10/2.5 mg/kg (15-40 kg); 400/100 mg/kg (> 40 kg)<br>ART-experienced: FTC (same dosage as above) plus background ART medications (no 3TC)<br>No control regimen | 96 weeks | Enrolled: 117<br>ITT: 116<br>ART-naive: 71<br>ART-experienced: 45<br>Age groups:<br>3–24 mo: 16<br>25 mo–6 y: 68<br>7–12 y: 29<br>13–17 y: 3 | Pediatric subjects (3 mo-17 y) with HIV infection, CD4+ > 200 cells/mm3;<br>ART-naive: Plasma HIV-1 RNA 5,000-600,000 copies/mL<br>ART-experienced: HIV-1 RNA ≤ 400 copies/mL, stable on 3TC regimen for ≥ 3 mo | Study completed;<br>m5.3.5.2<br>Final Week 48 CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | FTC-301A (synopsis) | Compare the safety and efficacy of FTC and d4T within a triple drug combination containing ddI and EFV | Phase 3, randomized (1:1), double-blind, active-controlled equivalence study | • FTC 200 mg QD PO (A)<br>• d4T 40 mg BID PO if ≥ 60 kg; 30 mg BID PO if < 60 kg (B)<br>Both groups: ddI 400 mg QD PO if ≥ 60 kg; 250 mg QD PO if < 60 kg and EFV 600 mg QD PO | 48 weeks: Last subject completed 48 weeks on 24 Oct 2002; all subjects subsequently rolled to an open-label FTC-containing regimen or an alternative regimen off study | Randomized and received ≥ 1 dose of study drug (ITT): 571<br>A: 286<br>B: 285 | HIV infected, ART-naive subjects | Study completed;<br>m5.3.5.1<br>Interim Week 48 CSR (Volume 1 and Volume 2) |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | FTC-302 (synopsis) | Compare the safety and efficacy of FTC to 3TC when used in combination d4T and either NVP orEFV | Phase 3, randomized (1:1), partially blinded, open-label, active-controlled study | Subjects were stratified per HIV-1 RNA levels, then randomized (1:1) to either FTC or 3TC (placebo blinded) plus open-label background therapy consisting of d4T[a] plus either NVP[b] or EFV and received:<br>• FTC 200 mg QD PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 194) or EFV 600 mg QD PO (n = 40) (A)<br>• 3TC 150 mg BID PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg BID and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 191) or EFV 600 mg once daily PO (n = 43) (B) | 48 weeks | Randomized: 512<br>ITT: 468<br>A: 234<br>B: 234 | HIV infected, ART-naive adult subjects | Study completed;<br><br>m5.3.5.1 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | FTC-303 (synopsis) | Compare FTC to 3TC in HIV infected subjects with HIV-1 RNA ≤ 400 copies/mL on a stable (≥ 12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI | Phase 3, randomized (2:1) open-label, multi-center equivalence study | • Subjects switch from 3TC to FTC PO while continuing on current background therapy (A)<br>• Subjects continue on current 3TC-containing regimen (B) | 48 weeks | Randomized: 459<br>ITT: 440<br>A: 294<br>B: 146 | HIV infected, 3TC-experienced, adult subjects with stable HIV-1 RNA | Study completed;<br>m5.3.5.1<br>Final CSR and Addendum |
| Intrinsic Factor PK | FTCB-101 (synopsis) | Assess the safety, tolerance, antiviral activity, and PK of FTC | Phase 1, open-label, dose-escalation, multiple repeat doses, 8 week study | • FTC 25 mg QD PO<br>• FTC 50 mg QD PO<br>• FTC 100 mg QD PO<br>• FTC 200 mg QD PO<br>• FTC 300 mg QD PO | 56 days with 28 day follow up | Enrolled: 49<br>Completed: 45<br>Safety Analysis Set: 49 | HBV-infected adult subjects | Study completed;<br>m5.3.3.3<br>Final CSR |

a. Subjects were allowed to switch from d4T to AZT if toxicity occurred
b. Subject were allowed to switched from NVP to EFV if toxicity occurred

## 1.6. FTC/TDF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-174-0105 (synopsis) | Evaluate the PK interactions between FTC/TDF FDC and TCL when administered alone and together | Single-center, open-label, randomized, 3-way crossover study | Subjects received each of the following treatments:<br>• FTC/TDF (200/300 mg) QD PO<br>• TCL 0.1 mg/kg/day in 2 divided doses BID PO | 21 days (7 days FTC/TDF FDC, 7 days TCL, 7 days FTC/TDF FDC + TCL) | Enrolled: 31<br>Completed: 21<br>Safety Analysis Set: 31 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR |

## 1.7. TDF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-99-903 (synopsis) | To assess the equivalence of TDF+ Lamivudine + Efavirenz versus Stavudine + Lamivudine + Efavirenz in the treatment of HIV-1-infected antiretroviral-naive patients as determined by the proportion of patients in each regimen with plasma HIV-1 RNA <400 copies/mL at week 48. | Phase 3, randomized, double-blind, parallel, multicenter, active-controlled study followed by an open-label phase | Test product:<br>TDF 300 mg QD, stavudine placebo BID, lamivudine 150 mg BID, efavirenz 600 mg QD.<br>Reference therapy:<br>TDF placebo QD, stavudine 40/30 mg BID, lamivudine 150 mg BID, efavirenz 600 mg QD. | Double-blind phase: 144 weeks<br>Open-Label phase: 96 weeks | Blinded phase:<br>ITT:<br>TDF+3TC+EFV: 299<br>D4T+3TC+EFV: 301 | HIV-1–infected ART-naive patients with plasma HIV-1 levels > 5000 copies/mL | Study completed;<br>m5.3.5.1<br>Final 144 week CSR |

## 1.8. FTC/RPV/TDF

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Comparative BA/BE | GS-US-264-0103<br>(synopsis) | Evaluate the bioequivalence of 2 FDC tablet formulations containing FTC/RPV/TDF (200/25/300 mg) compared to FTC 200 mg + RPV 25 mg + TDF 300 mg and evaluate the safety of coadministered FTC, RPV, and TDF as FDC tablet or individual dose forms. | Phase 1, randomized, open-label, single-center, single-dose, 3-way crossover study | Subjects were randomized to 1 of 6 treatment sequences and received a single dose of each treatment (separated by a 14-day washout period):<br>• FTC 200-mg capsule + RPV 25-mg tablet + TDF 300 mg tablet (A)<br>• FTC/RPV/TDF (200/25/300 mg) test formulation 3 FDC tablet (B)<br>• FTC/RPV/TDF (200/25/300 mg) test formulation 4 FDC tablet (C) | 3 single doses (Days 1, 15, and 29) | Randomized: 36<br>Completed: 34<br>Safety Anaysis Set: 35<br>A: 35<br>B: 34<br>C: 35<br>PK Analysis Set: 34 | Healthy adult subjects | Study completed;<br>m5.3.1.2 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Study Pertinent to the Claimed Indication | GS-US-264-0106 (synopsis) | Primary Objective:<br>Evaluate the noninferiority of FTC/RPV/TDF STR relative to regimens consisting of a PI/r and 2 NRTIs in maintaining HIV-1 RNA < 50 copies/mL at Week 24<br>Secondary Objectives:<br>Evaluate the change from baseline in fasting lipid parameters over 24 and 48 weeks<br>Evaluate the safety and tolerability of each treatment over 24 and 48 weeks<br>Evaluate the change from baseline in CD4+ cell count in each treatment group at 24 and 48 weeks | Phase 3b, randomized, open-label, multicenter study | FTC/RPV/TDF (200/25/300 mg) STR administered orally with a meal once daily for 48 weeks<br>Delayed Switch:<br>Baseline ARV drug regimen consisting of a PI/r and 2 NRTIs administered orally for 24 weeks (SBR group) followed by FTC/RPV/TDF (200/25/300 mg) STR administered orally with a meal once daily for 24 weeks | 48 weeks [a] | FTC/RPV/TDF: 317<br>SBR (baseline ARV regimen for 1st 24 weeks): 159<br>Delayed Switch: 152 | Adult HIV-1 infected subjects receiving ARV therapy consisting of a PI/r and 2 NRTIs, with undetectable HIV-1 RNA for ≥ 6 months prior to screening and HIV-1 RNA < 50 copies/ mL at screening. | 48-week randomized treatment period complete; m5.3.5.1 Final CSR |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Study Pertinent to the Claimed Indication | GS-US-264-0111 (synopsis) | Primary Objective:<br>Evaluate the efficacy of FTC/RPV/TDF STR after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/mL at Week 12<br>Secondary Objectives:<br>Evaluate the safety and tolerability of FTC/RPV/TDF STR over 24 and 48 weeks<br>Evaluate the efficacy of FTC/RPV/TDF STR after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/mL at Weeks 24 and 48<br>Explore the PK of RPV after switching from EFV | Phase 2b, open-label, multicenter, pilot study | FTC/RPV/TDF (200/25/300 mg) STR administered orally with a meal once daily | 48 weeks | Enrolled: 50<br>Safety Analysis Set: 49<br>EFV PK Analysis Set: 49<br>RPV PK Analysis Set: 49 | HIV-1 infected adults receiving a first ARV regimen consisting of EFV/FTC/TDF for ≥ 3 months prior to screening who decided on a change of regimen due to EFV intolerance. Subjects must have maintained plasma HIV-1 RNA at undetectable levels while on treatment for ≥ 8 weeks prior to screening. | Study complete m5.3.5.1 Final CSR |

a In countries where FTC/RPV/TDF STR was not commercially available at the end of Week 48, subjects did not complete the scheduled 30-day follow-up visit, and instead were allowed to continue to receive FTC/RPV/TDF STR until it became commercially available, or until Gilead elected to terminate clinical development of FTC/RPV/TDF STR in that country.

## 1.9. RPV

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PK and Tolerability | R278474-CDE-101 (CDE-101) (synopsis) | Evaluate the safety, tolerability, PK, and ex vivo pharmacodynamics of single ascending doses of R278474 | Phase 1, randomized, double-blind, placebo-controlled, single dose, multiple-sequential group, dose escalation study | Subjects were sequentially enrolled into 3 groups (n = 9), then randomized (2:1) to a single dose of R278474 or placebo:<br>• Group A: R278474 12.5 mg/ oral solution or placebo (fed)<br>• Group B: R278474 25 mg oral solution or placebo (fed)<br>• Group C: R278474 50 mg oral solution or placebo (fed) | Single Dose | Randomized: 27<br>Completed: 27<br>R278474: 18<br>Placebo: 9 | Healthy male subjects | Study completed;<br>m5.3.3.1 Final CSR[a] |
| Healthy Subject PK and Tolerability | R278474-CDE-102 (CDE-102) (synopsis) | Evaluate the safety, tolerability, PK, and ex vivo pharmacodynamics of R278474 following multiple oral doses | Phase 1, randomized, double-blind, placebo-controlled, multiple dose, multiple-sequential group, dose escalation study | Subjects were sequentially enrolled into 3 groups (n = 9), then randomized (2:1) to either oral solution or placebo:<br>• Group A: R278474 25 mg oral solution or placebo (fed)<br>• Group B: R278474 75 mg oral solution or placebo (fed)<br>• Group C: R278474 150 mg oral solution or placebo (fed) | 14 days | Randomized: 27<br>Completed: 26<br>R278474: 17<br>Placebo: 9 | Healthy male subjects | Study completed;<br>m5.3.3.1 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PK and Tolerability | R278474-CDE-103 (CDE-103) (synopsis) | Evaluate the safety, tolerability, PK, and ex vivo pharmacodynamics of R278474 following single ascending oral doses | Phase 1, randomized, double-blind, placebo-controlled, multiple-sequential group, dose escalation study | 4 groups (n = 9) were sequentially enrolled; subjects within each group were randomized (2:1) to a single dose of R278474 or placebo:<br>• Group A: R278474 50 mg oral solution or placebo (fed)<br>• Group B: R278474 100 mg oral solution or placebo (fed)<br>• Group C: R278474 200 mg oral solution or placebo (fed)<br>• Group D: R278474 300 mg oral solution or placebo(fed) | Single Dose | Randomized: 36<br>Completed: 36<br>R278474: 24<br>Placebo: 12 | Healthy male subjects | Study completed;<br>m5.3.3.1 Final CSR[a] |
| Healthy Subject PK and Tolerability | TMC278-C103 (C103) (synopsis) | Evaluate the safety, tolerability and PK of the solid formulation | Phase 1, randomized, open-label, parallel group, multiple-dose-ranging study | Subjects were randomized to 1 of 4 parallel panels and received either:<br>• TMC278 25-mg tablet once daily under fed conditions (A)<br>• TMC278 50 mg (2 × 25-mg tablets) once daily under fed conditions (B)<br>• TMC278 100-mg tablet once daily under fed conditions (C)<br>• TMC278 150 mg (1 ×100-mg and 2 × 25-mg tablets) once daily under fed conditions (D) | 14 days | Randomized:48<br>Completed: 46<br>A: 12<br>B: 12<br>C: 11<br>D: 11 | Healthy adult subjects | Study completed;<br>m5.3.3.1 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | R278474-C108 (C108) (synopsis) | Evaluate the effect of steady-state rifampin on the steady state PK of TMC278, and to investigate the effect of steady state TMC278 on the steady-state PK of rifampin and its active metabolite 25-desacetylrifampin | Phase 1, randomized, open-label, 3-way crossover study | Subject received 3 treatments (with a 14-day washout period between treatments) in a randomized sequence and received the following (under fed conditions):<br>• TMC278 150 mg oral solution daily for 7 days (A)<br>• Rifampin 600mg (2 ×300 mg oral capsules) daily for 7 days (B)<br>• TMC278 150 mg oral solution and rifampin 600 mg (2 ×300 mg oral capsules) daily for 7 days (C) | 21 days (Subjects received each treatment for 7 days, with a 14-day washout period between treatments) | Enrolled: 16<br>Completed: 15<br>A: 15<br>B: 16<br>C: 16 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |
| Extrinsic Factor PK | TMC278-C109 (C109) (synopsis) | Determine the effect of steady-state (multiple dose) TMC278 concentrations on the PK of paracetamol and the effect of paracetamol on the steady-state PK of TMC278 | Phase 1, randomized, open-label, 2-way crossover, multiple-dose, drug interaction study | Subjects were randomized to 1of 2 treatment sequences (AB or BA) and received the following (under fed conditions):<br>• Single dose of paracetamol 500 mg (A)<br>• TMC278 150 mg daily (Days 1 to 11) plus a single dose of 500 mg paracetamol on Day 11 (B) | A: 1 day<br>B: 11 days (TMC278: 11 days, paracetamol: 1 day) | Enrolled: 16<br>Completed: 16 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC435-TiDP16-C114<br>(C114)<br>(synopsis) | Evaluate the effect of steady-state concentrations of TMC435 on steady-state PK of TMC278 (Panel 1) or TDF (Panel 2), to evaluate the effect of steady-state concentrations of TMC278 on steady-state PK of TMC435, and to evaluate the effect of steady-state concentrations of TDF on PK of steady-state TMC435 | Phase 1, randomized, open-label, 3-way crossover study | Subjects were enrolled into 1 of 2 panels, then randomized to 1 of 6 treatment sequences per panel (Panel 1: ABC, BCA, CAB, CBA, BAC, and ACB; Panel 2: DEF, EFD, FDE, FED, EDF, and DFE) with a washout period (14 and 7 days, respectively) between each treatment and received the following (under fed conditions):<br>Panel 1:<br>• TMC435 150 mg (2 × 75-mg capsules) QD for 11 days (A)<br>• TMC278 25 mg (1 × 25-mg tablet) QD for 11 days (B)<br>• TMC435 150 mg (2 × 75-mg capsules) plus TMC278 25 mg (1 × 25-mg tablet) QC for 11 days (C)<br>Panel 2:<br>• TMC435 150 mg (2 × 75-mg capsules) QD for 7 days (D)<br>• TDF 300 mg (1 × 300-mg tablet) QD for 7 days (E)<br>• TMC435 150 mg (2 × 75-mg capsules) plus TDF 300 mg (1 × 300-mg tablet) QD for 7 days (F) | Panel 1: 60 days (11 days per treatment)<br>Panel 2: 34 days (7 days per treatment) | Enrolled and randomized: 48<br>Completed: 45<br>Safety Analysis Set: 48<br>A: 21<br>B: 23<br>C: 22<br>D: 24<br>E: 24<br>F: 24 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278-C116 (C116) (synopsis) | Determine the effect of steady-state (multiple dose) TMC278 concentrations on the steady-state PK of atorvastatin, atorvastatin lactone, and the active metabolites 2-hydroxyatorvastatin and 4-hydroxyatorvastatin, and the effect of steady-state atorvastatin concentrations on the steady-state PK of TMC278 | Phase 1, randomized, open-label, 2-way crossover, multiple-dose, drug interaction study | Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following (under fed conditions):<br>• Single dose of atorvastatin 40 mg (A)<br>• TMC278 150 mg daily (Days 1 to 15) plus 40 mg atorvastatin daily on Days 12 to 15 (B) | 19 days (excluding 14-day washout period)<br>A: 4 days<br>B: 15 days (TMC278 Days 1 to 15, atorvastatin Days 12 to 15) | Enrolled: 16<br>Completed: 16<br>Safety Analysis Set: 16 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Comparative BA/BE | TMC278-C117 (synopsis) | Compare the oral bioavailability of the 2 reference Phase 2b tablet formulations with the newly developed Phase 3 tablet formulation | Phase 1, randomized, open-label, 2-way crossover, single-dose study | Subjects were randomized to 1 of 2 treatment sequences within Panels 2 and 3 (Panel 1 was removed prior to treatment) and received :<br>Panel 2:<br>• TMC278 (Phase 3 formulation) 100 mg (4 × 2- mg tablets) PO, single dose under fed conditions (C)<br>• TMC278 (Phase 2b formulation) 100 mg (1× 100-mg tablet) PO, single dose under fed conditions (D)<br>Panel 3:<br>• TMC278 (Phase 3 formulation) 150 mg (1 × 150-mg tablet) PO, single dose under fed conditions (E)<br>• TMC278 (Phase 2b formulation) 150 mg (3 × 50-mg tablets) PO, single dose under fed conditions (F) | 2 single doses (separated by 13-day washout period) | Enrolled: 32<br>Completed: 32<br>Safety Analysis Set: 32 | Healthy adult subjects | Study completed;<br>m5.3.1.2<br>Final CSR[a] |
| Healthy Subject PK and Tolerability | TMC278-C119 (C119) (synopsis) | Characterize absorption, distribution, excretion, and the overall metabolic profile of a single dose of $^{14}$C-radiolabeled TMC278 | Phase 1, open-label, single dose, mass-balance study | Subjects received a single dose of $^{14}$C-radiolabeled and unlabeled TMC278 150 mg administered as an oral solution under fed conditions. | Single Dose | Enrolled: 6<br>Completed: 6<br>Safety Analysis Set: 6 | Healthy male subjects | Study completed;<br>m5.3.3.1<br>Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278-TiDP6-C121 (C121) (synopsis) | Determine the effect of steady-state (multiple dose) TMC278 concentrations on the steady-state PK of R- and S-methadone | Phase 1, open-label, single-sequence, multiple dose, drug interaction study | Subjects received methadone per individualized maintenance therapy (between 60 and 150 mg) daily (Days −14 to 12 coadministered with TMC278 25 mg oral tablet daily under fed conditions (Days 1 to 11) | 25 days:<br>TMC278: 11 days<br>methadone: 25 days | Enrolled: 13<br>Completed: 12<br>Safety Analysis Set: 13[b] | HIV-negative subjects on stable methadone maintenance therapy | Study completed;<br>m5.3.3.4 Final CSR[a] |
| Extrinsic Factor PK | TMC278-TiDP6-C123 (synopsis) | Determine the effect of steady-state (multiple dose) TMC278 concentrations on the single dose PK of sildenafil and its active metabolite N-desmethyl sildenafil and the effect of single dose sildenafil concentrations on the steady-state PK of TMC278 | Phase 1, randomized, open-label, 2-way crossover, multiple-dose, drug interaction study | Subjects were randomized to 1 of 2 treatment sequences and received treatment under fed conditions:<br>• Single dose of sildenafil 50 mg oral tablet (A)<br>• TMC278 75 mg oral tablet daily for 12 days plus a single dose of sildenafil 50 mg on Day 12 (B) | 13 days:<br>A: 1 day<br>B: 12 days<br>• TMC278: 12 days<br>• Sildenafil: 1 day | Enrolled: 16<br>Completed: 15<br>Safety Analysis Set: 16<br>A: 15<br>B: 16 | Healthy male subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |
| Extrinsic Factor PK | TMC278-C127 (C127) (synopsis) | Determine the effect of steady-state (multiple dose) TMC278 concentrations on the steady-state PK of ketoconazole and the effect of steady-state ketoconazole concentrations on the steady-state PK of TMC278 | Phase 1, randomized, open-label, 2-way crossover, multiple-dose, drug interaction study | Subjects were randomized to 1 of 2 treatment sequences (with a 14-daywashout period between) and received treatment under fed conditions:<br>• TMC278 150 mg (1 × 100- and 1 × 50 mg oral tablet) once daily (A)<br>• ketoconazole 400 mg (2 × 200 mg oral tablets) plus TMC278 150 mg (1 × 100- and 1 × 50 mg oral tablet) once daily (B) | 33 days:<br>A: 11 days<br>B: 22 days<br>ketoconazole: 22 days<br>TMC278: Days 12 to 22 | Randomized: 16<br>Completed: 14<br>A: 15<br>B: 14 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Intrinsic Factor PK | TMC278-TiDP6-C130<br>(C130)<br>(synopsis) | Determine the single dose and steady-state (multiple dose) PK and short term safety and tolerability of TMC278 in subjects with mild or moderate hepatic impairment compared to matched healthy control volunteers | Phase 1, open-label, parallel group, controlled, sequential, multiple-dose study. | Subjects were enrolled based on hepatic impairment and received TMC278 25 mg-tablet once daily under fed conditions | 11 days | Enrolled and Completed: 32<br>Mild hepatic impairment: 8<br>Moderate hepatic impairment: 8<br>Healthy control: 16 | Subjects with mild or moderate hepatic impairment and healthy volunteers | Study completed;<br>m5.3.3.3 Final CSR[a] |
| Healthy Subject PD and PK/PD | TMC278-TiDP6-C131<br>(C131)<br>(synopsis) | Evaluate the effect of single-dose and steady-state administration of TMC278, compared to placebo, on the QT/QTcF interval | Phase 1, randomized, double-blind, double-dummy, placebo- and active-controlled, 3-way crossover, multiple-dose study | Subjects were randomized to 1 of 6 treatment sequences and received treatment under fed conditions (separated by a 21-day washout period):<br>• TMC278 75 mg (1 ×75 mg oral tablet) plus TMC278 placebo (3 tablets) once daily (Days 1 to 11) followed by a single dose of moxifloxacin placebo on Day 12 (A)<br>• TMC278 300 mg (4 ×75 mg oral tablets) once daily (Days 1 to 11) followed by a single dose of moxifloxacin placebo on Day 12 (B)<br>• TMC278 placebo (4 tablets) once daily (Days 1 to 11) followed by a single dose of 400 mg moxifloxacin capsule on Day 12 (C) | 12 days per treatment | Randomized: 41<br>Completed: 38<br>Safety Analysis Set: 41<br>A: 40<br>B: 40<br>C: 39 | Healthy adult subjects | Study completed;<br>m5.3.4.1 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278-TiDP6-C136<br>(C136)<br>(synopsis) | Determine the effect of steady-state (multiple dose) TMC278 concentrations on the steady-state PK of ethinylestradiol and on the steady-state PK of norethindrone | Phase 1, open-label, single-sequence, multiple-dose, drug interaction study | Subjects were to stabilized to 35 µg ethinylestradiol/1.0 mg norethindrone (OC) for one 28-day cycle (including a 7-day pill-free period), and received the following treatments (under fed conditions) in sequential order:<br>• ethinylestradiol/norethindrone (35 µg /1.0 mg) oral tablet once daily 21-days (A)<br>• ethinylestradiol/norethindrone (35 µg /1.0 mg) oral tablet once daily for 21 days plus TMC278 25-mg tablet once daily Days 29 to 43 (B) | 84 days: Stabilizing Treatment (1st cycle): OC 21 days, followed by a 7 day pill-free period<br>A (2nd cycle): OC 21 days, followed by a 7 day pill-free period<br>B (3rd cycle):OC: Days 29 to 49 plus TMC278: Days 29 to 43 (fed) | Enrolled: 18<br>Completed: 13<br>Safety Analysis Set: 18<br>A: 18<br>B: 16 | Healthy female subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |
| Extrinsic Factor PK | TMC278-C139<br>(C139)<br>(synopsis) | Determine the effect of single dose and steady-state (multiple dose) TMC278 concentrations on the PK of chlorzoxazone and 6-hydroxy-chlorzoxazone after a single dose of chlorzoxazone, and the effect of single dose chlorzoxazone concentrations on the steady-state PK of TMC278 | Phase 1, open-label, multiple dose, drug interaction study[c] | Main study: single dose of chlorzoxazone 500 mg on Days 1, 4 and 15 or 19 and once daily dose of TMC278 150 mg (1 × 100- and 1 × 50-mgtablet) on Days 4 to 15 or Days 4 to 19 (fed)<br>Sub-study: single dose of chlorzoxazone 500-mg tablet on Days 1, 4, and 19 and once daily dose of TMC278 150 mg (1 × 100- and 1 × 50-mg tablet) on Days 4 to 19 (fed) | 13 or 17 days, excluding washout (2 days), (due to extreme weather conditions [hurricane] some subjects received 4 additional days of TMC278 dosing) | Randomized: 25<br>Main protocol: 16<br>Substudy: 9<br>Completed: 19<br>Main protocol: 10<br>Substudy: 9 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278-C140 (C140) (synopsis) | Determine the effect of single dose famotidine concentrations on the single dose PK of TMC278 in 3 different dosing regimens and investigate the relationship between intragastric pH and the PK of TMC278 | Phase 1, randomized, open-label, 4-way crossover, single-dose, drug interaction study | Subjects were randomized to 1 of 4 treatment sequences (ADBC, BACD, CBDA, or DCAB) and received a single dose (separated by a 14-day washout period) of the following:<br>• Treatment A: single dose of TMC278 150 mg (fed)<br>• Treatment B: single dose of famotidine 40 mg, (fasted) and a single dose of TMC278 150 mg 2 hours later (fed)<br>• Treatment C: single dose of TMC278 150 mg (fed) and a single dose famotidine 40 mg 4 hours later (fed)<br>• Treatment D: single dose of famotidine 40 mg (fed[d]) and a single dose of TMC278 150 mg 12 hours later (fed ) | 4 days:<br>Single dose per treatment | Randomized: 24<br>Completed: 23<br>Safety Analysis Set: 24 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PD and PK/PD | TMC278-TiDP6-C151 (C151) (synopsis) | Evaluate the effect of TMC278 at steady-state, compared to baseline, on the QT/QTcF interval | Phase 1, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel group, multiple-dose study | Subjects were randomized to either:<br>• TMC278 25-mg tablet once daily (Days 1 to 11) and a single dose of moxifloxacin placebo on Day 12, under fed conditions (A)<br>• TMC278 placebo tablet once daily (Days 1 to 11) and a single dose of moxifloxacin 400-mg capsule on Day 12, under fed conditions (B) | 12 days | Randomized and completed: 36<br>A: 24<br>B: 12 | Healthy adult subjects | Study completed;<br>m5.3.4.1 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Healthy Subject PD and PK/PD | TMC278-TiDP6-C152 (C152) (synopsis) | Evaluate the effect of TMC278 at steady-state and the effect of EFV at steady-state on the QT/QTcF interval, in 2 randomized panels | Phase 1, randomized, double-blind, double-dummy, placebo- and active-controlled, crossover, multiple-dose study | Subjects were randomized (1:1) to 1 of 2 panels and received all panel treatments in randomized sequence :<br>TMC278 Panel:<br>• Treatment A: TMC278 25-mg tablet daily (Days 1-11) plus moxifloxacin placebo, under fed conditions (Day 11)<br>• Treatment B: TMC278 placebo (Days 1 to 11) plus moxifloxacin placebo, under fed conditions (Day 11)<br>• Treatment C: TMC278 placebo (Days 1 to 11) plus moxifloxacin 400-mg capsule, under fed conditions<br>EFV Panel:<br>• Treatment D: EFV 600-mg tablet daily, under fasted conditions (Days 1 to 11)<br>• Treatment E: EFV placebo daily, under fasted conditions (Days 1 to 11) | TMC278 Panel: 33 days (three 11 day periods separated by 21-day washout periods)<br>EFV Panel: 22 days (two11 day periods separated by a 53-day washout period) | Randomized and treated: 120<br>TMC278 Panel: 60<br>EFV Panel: 60<br>Completed: 106<br>TMC278 Panel: 56<br>EFV Panel: 50 | Healthy adult subjects | Study completed;<br>m5.3.4.1 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278-TiDP6-C154 (C154) (synopsis) | Evaluate the PK of TMC278 at doses of 25 and 50 mg in the presence of omeprazole 20 mg and to evaluate the relationship between intragastric pH and the PK of TMC278 | Phase 1, open-label, randomized, 4-way cross-over study | Subjects were randomized to 1 of 4 treatment sequences (ADBC, BACD, CBDA, or DCAB) and received all treatments, separated by a ≥14-day washout period:<br>• Single dose of TMC278 25 mg in the morning, under fed conditions (A)<br>• Omeprazole 20 mg in the morning for 7 days under fasted conditions plus a single dose of TMC278 25 mg in the morning under fed conditions on Day 6 (B)<br>• Omeprazole 20 mg in the evening for 6 days under fasted conditions plus a single dose of TMC278 25 mg in the morning under fed conditions on Day 6 (C)<br>• Omeprazole 20 mg in the morning for 7 days under fasted conditions plus a single dose of TMC278 50 mg (2 × 25-mg tablets) in the morning under fed conditions on Day 6 (D) | 21 days;<br>TMC278: 4 single doses<br>Omeprazole: 20 days (6 to 7 days per treatment) | Randomized: 18<br>Completed: 15<br>Safety Analysis Set: 17<br>Omeprazole: 17<br>TMC278: 16 | Health adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | R278474-C201 (C201) (synopsis) | Evaluate the change from baseline in plasma viral load during treatment with multiple dose (once daily) TMC278 as functional monotherapy | Phase 2a, randomized, double-blind, placebo-controlled, dose-escalation, proof-of-principle, multiple-dose study | Subjects were randomized in a 3:1 ratio (active:placebo) to 1 of 4 dose panels:<br>• Panel 1: once daily dose of TMC278 25 mg oral solution or matching placebo, (fed)<br>• Panel 2: once daily dose of TMC278 50 mg oral solution or matching placebo, (fed)<br>• Panel 3: once daily dose of TMC278 100 mg oral solution or matching placebo, (fed)<br>• Panel 4: once daily dose of TMC278 150 mg oral solution or matching placebo, (fed) | 7 days | Enrolled and analyzed: 47<br>Completed: 46*<br>*47 subjects completed treatment and one was lost to follow-up | HIV-infected, treatment naïve male subjects (with documented absence of resistance) | Study completed;<br>m5.3.5.1<br>Final CSR[a] |
| Uncontrolled Clinical Studies | R278474-C202 (C202) (synopsis) | Evaluate the change from baseline in plasma viral load during treatment with multiple dose (once daily) TMC278 as functional monotherapy | Phase 2a, randomized, open-label, proof-of-principle, multiple dose study | Subjects received their NtRTI background regimen (plus enfuvirtide if applicable) in combination with either:<br>• TMC278 25 mg oral solution daily, under fed conditions (A)<br>• TMC278 50 mg oral solution daily, under fed conditions (B)<br>• TMC278 150 mg oral solution daily, under fed conditions (C) | 7 days | Randomized:38<br>Completed: 33<br>Safety Analysis Set: 36<br>A: 13<br>B: 12<br>C: 11 | HIV-1 infected subjects with NNRTI experience and/or genotypic evidence of NNRTI resistance associated mutations | Study completed,<br>m5.3.5.2<br>Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Control-led Clinical Study Pertinent to the Claimed Indication | TMC278-C204 (C204) (synopsis) | Evaluate the dose-response relationship of antiviral efficacy after 48 weeks of treatment with 3 different doses of RPV | Phase 2b, randomized, active-controlled, partially blinded, dose-finding study | Subjects were randomized to 1 of 4 treatment groups and received investigator-selected background N(t)RTI regimen (AZT/3TC or FTC/TDF) plus either:<br>• TMC278 25-mg tablet, under fed conditions<br>• TMC278 75 mg (1 × 50-mg and 1 × 25-mg tablet), under fed conditions<br>• TMC278 150 mg (1 × 100-mg and 1 × 50-mg tablet), under fed conditions<br>• EFV 600-mg tablet, under fasted conditions | 96 week dose-finding phase of partially blinded (RPV groups) or unblinded (control group) treatment, followed by 3 open-label extension treatment periods (Weeks 96-144, 144-240, and > 240) | Randomized and treated: 368<br>RPV 25 mg: 93<br>RPV 75 mg: 95<br>RPV 150 mg: 91<br>Control: 89<br>Ongoing Weeks 96-144: 273<br>All RPV:208<br>Control: 65<br>Ongoing Weeks 144-240: 251<br>All RPV: 191<br>Control: 60<br>Ongoing > Week 240: 148<br>All RPV: 148<br>Control: 0 | HIV-1 infected, ARV treatment-naive adults | Study completed;<br>m5.3.5.1<br>Week 48 CSR[a]<br>Week 96 CSR[a]<br>Week 192 CSR[a]<br>Week 240 (Final) CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Control-led Clinical Study Pertinent to the Claimed Indication | TMC278-TiDP6-C209 (C209, ECHO) (synopsis) | Primary objective is to demonstrate noninferiority of RPV vs EFV (control) in regard to the proportion of subjects achieving a confirmed plasma viral load of < 50 HIV-1 RNA copies/mL at 48 weeks, according to the TLOVR algorithm, with a maximum allowable difference of 12% | Phase 3, international, randomized, double-blind double-dummy, active-controlled study | • Tablets containing RPV 25 mg under fed conditions QD PO plus placebo EFV under fasted conditions QD PO, plus background N(t)RTI regimen of FTC/TDF<br>• Tablets containing EFV 600 mg under fasted conditions QD PO plus placebo RPV under fed conditions QD PO plus background N(t)RTI regimen of FTC/TDF<br>Subjects receiving active RPV under fed conditions also took placebo EFV under fasted conditions (and vice versa) in addition to their background regimen. | 96 weeks of double-blind treatment, followed by a post 96-week double-blind treatment period (until all subjects had been treated for at least 96 weeks or discontinued earlier, and the Week 96 database was locked), followed by an open-label extension treatment period | Randomized and treated: 690<br>RPV: 346<br>Control:344<br>Completed Week 96: 550<br>RPV: 273<br>Control: 277<br>Ongoing into double-blind post 96-week treatment period: 542<br>RPV: 270<br>Control: 272 | HIV-1 infected, ARV treatment-naive adults | Study completed,<br>m5.3.5.1<br>Week 48 CSR[a]<br>Week 96 (pivotal) CSR[a] |
| Uncontrolled Clinical Studies | TMC278-TiDP38-C213 (C213; PAINT) (synopsis) | Determine the effect of steady-state (multiple dose) PK and short-term safety and efficacy of TMC278 in adolescents | Phase 2, open-label, single arm study | Once daily dose of TMC278 25 mg, under fed conditions, plus 2 investigator selected N(t)RTIs: AZT,ABC, or TDF in combination with 3TC or FTC (AZT/3TC, AZT/FTC, ABC/3TC, ABC/FTC, TDF/FTC, or TDF/3TC) | 48 Weeks | Randomized and Treated: 36<br>Completed: 4<br>Ongoing: 24 | HIV-1 infected treatment naïve adolescents (12 to < 18 years) | Study ongoing,<br>m5.3.5.2<br>Week 48 Interim CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Control-led Clinical Study Pertinent to the Claimed Indication | TMC278-TiDP6-C215 (C215, THRIVE) (synopsis) | Primary objective is to demonstrate noninferiority of RPV vs EFV (control) in regard to the proportion of subjects achieving a confirmed plasma viral load of < 50 HIV-1 RNA copies/mL at 48 weeks of treatment, according to the TLOVR algorithm, with a maximum allowable difference of 12% | Phase 3, international, randomized, double-blind, double-dummy, active-controlled study | • Tablets containing RPV 25 mg under fed conditions QD PO plus placebo EFV under fasted conditions, plus investigator-selected background N(t)RTI regimen of ABC/3TC, AZT/3TC, or FTC/TDF<br>• Tablets containing EFV 600 mg under fasted conditions QD PO plus RPV under fasted conditions, plus investigator-selected background N(t)RTI regimen of ABC/3TC, AZT/3TC, or FTC/TDF<br>Subjects receiving active RPV under fed conditions also took placebo EFV under fasted conditions (and vice versa) in addition to their background regimen. | 96 weeks of double-blind treatment, followed by a post 96-week double-blind treatment period (until all subjects had been treated for at least 96 weeks or discontinued earlier, and the Week 96 database was locked), followed by an open-label extension treatment period | Randomized and treated: 678 (RPV 340 and 338 control)<br>Completed Week 96: 549 (281 RPV and 268 control)<br>Ongoing into double-blind post 96-week treatment period: 545 (279 RPV and 266 control) | HIV-1 infected, ARV treatment-naive adults - | Study completed,<br>m5.3.5.1<br>Week 48 CSR[a]<br>Week 96 (pivotal) CSR[a] |
| Extrinsic Factor PK | TMC278 HIV1001 (synopsis) | Determine the PK of TMC278 following a 2-week period receiving EFV | Phase 1, open-label, single-arm study | Treatments A and B were separated by a 14-day washout period:<br>• TMC278 25-mg tablet, under fed conditions, for 14 days (A)<br>• EFV 600-mg tablet, under fasted conditions, for 14 days (B)<br>• TMC278 25-mg tablet, under fed conditions, for 28 days (C) | 56 days (excluding washout periods) | Enrolled: 20<br>Completed: 17<br>Safety Analysis Set: 20<br>A: 20<br>B: 20<br>C: 19 | Healthy adult subjects, excluding females of childbearing potential | Study completed;<br>m5.3.3.4<br>Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278IFD1001 (synopsis) | Evaluate the effect of steady-state TMC278 on the single dose PK of digoxin and determine short-term safety and tolerability of steady-state TMC278 coadministered with single dose digoxin | Phase 1, randomized, open-label, crossover study | Subjects were randomized to 1 of 2 treatment sequences (treatments separated by 14-day washout period) and received (under fed conditions):<br>• Digoxin 0.5 mg (2 × 0.25-mg tablets) on Day 1 (A)<br>• TMC278 25 mg tablet on Days 1 to 16 plus Digoxin 0.5 mg (2 × 0.25-mg tablets) on Day 11 (B) | 17 days<br>A: 1 day<br>B: 16 days | Randomized: 22<br>Completed: 21<br>Safety Analysis Set: 22<br>A: 21<br>B: 22 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |
| Extrinsic Factor PK | TMC278IFD1003 (synopsis) | Evaluate the PK of RPV 50 mg once daily in combination with rifabutin 300 mg daily, compared to the PK of RPV 25 mg daily alone in healthy adult subjects and to evaluate the PK of additional RPV doses in combination with rifabutin 300 mg daily compared to the PK of RPV 25 mg daily alone in healthy adult subjects | Phase 1, open-label, 3-period study | Subjects were randomized to 1 of 2 treatment sequences (ABC or BAC). Each treatment was administered under fed conditions, and followed by a 21-day washout period:<br>• RPV 25 mg QD administered on Days 1 to 11 (A)<br>• RPV 50 mg QD administered on Days 1 to 11 + rifabutin 300 mg QD administered on Days 1 to 17 (B)<br>• RPV (regimen was based on an interim PK analysis of Treatments A and B) administered on Days 1 to 11 + rifabutin 300 mg daily administered on Days 1 to 17 (C) | 45 days:<br>• RPV: 11 days per Treatment<br>• rifabutin: 17 days (Treatments B and C) | Randomized: 20<br>Completed: 10<br>A: 17<br>B: 12<br>C: 10<br>Safety Analysis Set: 20<br>A: 18<br>B: 20<br>C: 11 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | TMC278 IFD1004 (synopsis) | Evaluate the effect of steady-state RPV 25 mg once daily on the pharmacokinetics of a single dose of metformin in healthy adult subjects. | Phase 1, open-label study | All subjects received Treatments A and B, under fed conditions, in two sessions in a fixed, sequential order (AB), with a washout period of 4 days in between intakes in the 2 sessions:<br>• Single dose of metformin hydrochloride (HCl) 850 mg on Day 1 (A)<br>• RPV 25 mg QD from Day 5 to Day 17 with a single dose of metformin HCl 850 mg on Day 15 (B) | 19 days:<br>•Metformin HCI: single dose per treatment<br>• RPV: 13 days | Treated: 20<br>Completed: 20 | Healthy adult subjects | Study completed;<br>m5.3.3.4 Final CSR[a] |

a. Study is on file with dossier submitted by Tibotec/Janssen
b. 1 subject received TMC278 for 6 days only; subject was withdrawn due to behavioral issues
c. Due to extreme weather conditions (hurricane), a substudy was performed to ensure 16 evaluable subjects; in the substudy, the trial was repeated for 9 additional healthy subjects.
d. Famotidine was administered 2 hours after food

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**SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES**

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# DESCOVY®
# (EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/ TENOFOVIR ALAFENAMIDE)

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24 June 2016

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|---|---|---|---|---|---|---|---|---|
| Uncontrolled Clinical Studies | GS-US-292-0112 (synopsis) | Evaluate the effect of GEN on renal parameters | Phase 3, open-label, multicenter, multi-cohort study | GEN (E/C/F/TAF; 150/150/200/10 mg) QD PO | 144 weeks<br>Extension Phase: Subjects have option to continue study drug for another 48 weeks until GEN is commercially available, becomes available through an access program, or development is terminated | Enrolled: 252<br>Safety Analysis Set:<br>Cohort 1: 242<br>Cohort 2: 6<br>Continuing study drug at data cut date:<br>Cohort 1: 215<br>Cohort 2: 6 | HIV infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min<br>Cohort 1: ART-experienced<br>Cohort 2: ART-naive | Study ongoing; GS-US-292-0112 Week 96 Interim CSR |

ART = antiretroviral therapy; CSR = clinical study report; GEN = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated, Genvoya® (previously referred to as E/C/F/TAF); $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; HIV = human immunodeficiency virus; HIV-1 = HIV type 1; PO = orally; QD = once daily; TAF = tenofovir alafenamide;

**SECTION 2.7**
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**SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES**

# DESCOVY®
# (EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

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|---|---|---|---|---|---|---|---|---|
| Intrinsic Factor PK | GS-US-320-1615 (synopsis) | Evaluate the PK of TAF and its metabolite TFV in subjects with normal hepatic function and subjects with severe hepatic impairment | Phase 1, open-label, parallel-group, single-dose, multicenter study | Subjects were enrolled in 1 of 2 groups (normal hepatic function or severe hepatic impairment) and received the following treatment:<br>TAF 25 mg tablet orally | Single dose | Randomized: 20<br>Treated: 20<br>Completed study treatment: 20<br>10 subjects per group | Adult subjects with severe hepatic impairment (CPT C) and healthy matched control subjects | Study completed; GS-US-320-1615 Final CSR |

CPT C = Child-Pugh-Turcotte Class C; CSR = clinical study report; PK = pharmacokinetic(s); TAF = tenofovir alafenamide; TFV = tenofovir

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**SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES**

# DESCOVY®
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|---|---|---|---|---|---|---|---|---|
| Extrinsic Factor PK | GS-US-311-1790 (synopsis) | Evaluate the effect of DVY (F/TAF 200/25 mg FDC) or GS-9883 on the PK of a representative hormonal contraceptive medication, NGM/EE.<br>Evaluate the safety and tolerability of DVY or GS-9883 when given with a representative hormonal contraceptive medication, NGM/EE. | Phase 1, randomized, open-label, single-center, fixed sequence, multiple-dose, multiple-cohort study | **Part A:**<br>Lead-in period (Lead-in Days 1–28) with NGM/EE QD<br>**Part B:**<br>Cycle 1:<br>NGM/EE QD for Study Days 1–28<br>Cycle 2:<br>Subjects were randomized to 1 of 2 cohorts and received the following treatments:<br>Cohort 1: NGM/EE QD for Study Days 29–56 plus DVY on Study Days 29–42<br>Cohort 2: NGM/EE QD for Study Days 29–56 plus GS-9883 75 mg on Study Days 29–42<br>All treatments were administered QD in the morning with food. | 84 days | Randomized: 32<br>Treated: 32<br>Completed Study Treatment:<br>Cohort 1: 13<br>Cohort 2: 15 | Healthy adult female subjects | Study completed; GS-US-311-1790 Final CSR |

CSR = clinical study report; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); FDC = fixed-dosed regimen; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); NGM/EE = norgestimate/ethinyl estradiol; PK = pharmacokinetics; QD = once daily

**SECTION 2.7**
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**SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES**

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)
# SUBMISSION REF. NO.: ODE-16-080
# (STUDY GS-US-366-1160)

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11 October 2016

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# 1. LISTING OF CLINICAL STUDIES

| Type of Study | Study Number | Study Objective(s) | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-366-1160 (synopsis) | To evaluate the noninferiority of switching to the FTC/RPV/TAF FDC (ODE) compared to continuing the NNRTI regimen EFV/FTC/TDF FDC (ATR) in virologically suppressed HIV-1 infected subjects as determined by maintaining HIV-1 RNA < 50 copies/mL at Week 48 (US FDA-defined Snapshot Algorithm) | Phase 3b, randomized, double-blind, multicenter study | **Treatment Group 1:** ODE (FTC/RPV/TAF 200/25/25 mg) FDC tablet administered QD PO with food + placebo-to-match ATR (EFV/FTC/TDF 600/200/300 mg) FDC tablet QD PO on an empty stomach at bedtime<br>**Treatment Group 2:** ATR (EFV/FTC/TDF 600/200/300 mg) FDC tablet QD PO on an empty stomach at bedtime + placebo-to-match ODE (FTC/RPV/TAF 200/25/25 mg) FDC tablet administered QD PO with food | At least 96 weeks.<br>After the last subject completes the Week 96 visit, all subjects will attend the Unblinding Visit, at which point subjects will be given the option to receive open-label ODE for up to an additional 48 weeks or until Gilead Sciences elects to discontinue the study, whichever occurs first. | **Treatment Group 1:**<br>Randomized: 440<br>Safety Analysis Set and FAS: 438<br>**Treatment Group 2:**<br>Randomized: 441<br>Safety Analysis Set and FAS: 437 | HIV-1 infected subjects ≥ 18 years old who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on EFV/FTC/TDF FDC (ATR) | Study ongoing; Week 48 CSR |

ATR = Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate); CSR = clinical study report; EFV/FTC/TDF = efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla); FAS = Full Analysis Set; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC/RPV/TAF = emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey); NNRTI = nonnucleoside reverse transcriptase inhibitor; ODE = Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide); PO = by mouth; QD = once daily; RNA = ribonucleic acid; US = United States

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**SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES**

# ODEFSEY®
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# SUBMISSION REF. NO.: ODE-16-080
# (STUDY GS-US-366-1216)

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|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-366-1216 (synopsis) | To evaluate the noninferiority of switching to the FTC/RPV/TAF FDC (ODE) compared to continuing FTC/RPV/TDF FDC (CPA) in virologically suppressed HIV-1 infected subjects as determined by maintaining HIV-1 RNA < 50 copies/mL at Week 48 (US FDA-defined Snapshot Algorithm) | Phase 3b, randomized, double-blind, multicenter study | All treatments were administered QD PO with food at approximately the same time each day.<br>**Treatment Group 1:** ODE (FTC/RPV/TAF 200/25/25 mg) FDC tablet + placebo-to-match CPA (FTC/RPV/TDF 200/25/300 mg) FDC tablet<br>**Treatment Group 2:** CPA (FTC/RPV/TDF 200/25/300 mg) FDC tablet + placebo-to-match ODE (FTC/RPV/TAF 200/25/25 mg) tablet | At least 96 weeks.<br>After the last subject completes the Week 96 visit, all subjects will attend the Unblinding Visit, at which point subjects will be given the option to receive open-label ODE for up to an additional 48 weeks or until Gilead Sciences elects to discontinue the study, whichever occurs first. | **Treatment Group 1:**<br>Randomized: 316<br>Safety Analysis Set: 316<br>FAS: 316<br>**Treatment Group 2:**<br>Randomized: 316<br>Safety Analysis Set: 314<br>FAS: 313 | HIV-1 infected subjects ≥ 18 years old who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on FTC/RPV/TDF FDC (CPA) | Study ongoing; Week 48 CSR |

CPA = Complera®/Eviplera® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate); CSR = clinical study report; FAS = Full Analysis Set; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC/RPV/TAF = emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey); FTC/RPV/TDF = emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera/Eviplera); ODE = Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide); PO = by mouth; QD = once daily; RNA = ribonucleic acid; US = United States

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# SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES

# GENVOYA®
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|---|---|---|---|---|---|---|---|---|
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-292-0104 (synopsis) | Evaluate the efficacy of GEN versus STB | Phase 3, randomized, double-blind, active-controlled, multicenter study | GEN + placebo-to-match STB QD PO (A)<br>STB + placebo-to-match GEN QD PO (B) | 144 weeks<br>Open-Label Extension Phase:<br>Subjects have option to receive GEN until it is commercially available or development is terminated | Randomized: 872<br>Safety Analysis Set:<br>A: 435<br>B: 432<br>Continuing study drug at data cut date:<br>A: 377<br>B: 361 | HIV-infected, ART-naive adult subjects | Study ongoing; GS-US-292-0104 Week 144 |
| Controlled Clinical Studies Pertinent to the Claimed Indication | GS-US-292-0111 (synopsis) | Evaluate the efficacy of GEN versus STB | Phase 3, randomized, double-blind, active-controlled, multicenter study | GEN + placebo-to-match STB QD PO (A)<br>STB + placebo-to-match GEN QD PO (B) | 144 weeks<br>Open-Label Extension Phase:<br>Subjects have option to receive GEN until it is commercially available or development is terminated | Randomized: 872<br>Safety Analysis Set:<br>A: 431<br>B: 435<br>Continuing study drug at data cut date:<br>A: 356<br>B: 346 | HIV-infected, ART-naive adult subjects | Study ongoing; GS-US-292-0111 Week 144 |

ART = antiretroviral therapy; GEN = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated, Genvoya®; HIV = human immunodeficiency virus; PO = orally; QD = once daily; STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)